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Integrated structural and network-based characterization of ABL1 as a central hub in leukemia, using protein interaction and motif analysis with Biopython

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Abstract

Abelson tyrosine kinase 1 (ABL1) is a critical regulator of cell growth, DNA damage response, cytoskeletal remodeling, and apoptosis, and its dysregulation is central to the development of myeloid leukemia. In this study, an integrated structure-guided computational analysis was performed to characterize the human ABL1 kinase domain using the crystal structure PDB ID: 8I7S. Structural visualization and active-site mapping were conducted using RasMol, while hydrogen bond interactions and structural alignment were analyzed using PyMOL. Protein–protein interaction analysis using the STRING database identified ABL1 as a central signalling hub interacting with adaptor, regulatory, and oncogenic proteins, including CRK, GRB2, CRKL, CBL, ATM, STAT5B, and BCR, with high-confidence interaction scores (≥0.99). B-factor analysis highlighted flexible loop and regulatory regions near the active site, while root mean square deviation (RMSD) analysis demonstrated strong structural conservation of 8I7S compared to reference structures (0.247 Å with 7W7Y and 1.2 Å with 6XR6). Structure validation yielded a high overall quality score of 98.14, with localized deviations restricted to flexible regions. Ramachandran plot analysis, generated using BioPython, confirmed good stereochemical quality, with most residues occupying favoured conformational regions. Sequence and motif annotation using PROSITE identified conserved kinase-specific motifs, including the ATP-binding glycine-rich loop and a catalytic active-site motif, confirming the functional integrity of ABL1(kumari et al 2025).Overall, this comprehensive analysis establishes the structural reliability and functional relevance of ABL1, providing a robust foundation for structure-guided drug design and CRISPR-based therapeutic targeting in myeloid leukemia (Kumari et al., 2023-2025)

Keywords: Structural Bioinformatics, protein structural Alignment, Domain motif analysis, Leukemia signalling, Biopython, System Biology, Protein-protein Interaction.

I.Introduction

Abelson tyrosine kinase 1 (ABL1) is a non-receptor tyrosine kinase that plays a central role in regulating cell growth, cytoskeletal remodeling, DNA damage response, and apoptosis (Pendergast, 2002; Wang, 2014). Dysregulation of ABL1 signalling, particularly through the formation of the BCR–ABL fusion protein, is a hallmark of chronic myeloid leukemia (CML) and other myeloid malignancies (Rowley, 1973; Deininger et al., 2000).The oncogenic activity of BCR–ABL arises from constitutive activation of the ABL1 kinase domain, leading to aberrant phosphorylation-dependent signaling and uncontrolled cell proliferation (Daley et al., 1990; Ren, 2005). Due to its critical biological role, ABL1 has been extensively studied as a therapeutic target, and structural insights into its kinase domain have been instrumental in the development of tyrosine kinase inhibitors (TKIs) (Druker et al., 2001; Hantschel et al., 2012).High-resolution protein structures deposited in the Protein Data Bank (PDB) provide a reliable foundation for understanding kinase function, stability, and regulation at the molecular level (Berman et al., 2000). The recently solved crystal structure of the human ABL1 kinase domain (PDB ID: 8I7S) offers an opportunity to perform detailed structural and functional characterization of ABL1 using computational approaches.In addition to structural integrity, protein–protein interaction (PPI) networks play a crucial role in defining kinase-mediated signaling pathways (kumari et al). Network-based analyses using curated interaction databases such as STRING enable the identification of functional partners, adaptor proteins, and regulatory nodes

associated with disease progression (Szklarczyk et al., 2021).Computational techniques including active-site mapping, hydrogen bond analysis, B-factor profiling, RMSD-based structural alignment, Ramachandran plot validation, and motif/domain annotation are widely used to assess protein stability, flexibility, and functional conservation (Kleywegt & Jones, 1997; Lovell et al., 2003; Rose et al., 2017). Integration of these approaches allows comprehensive evaluation of protein quality and suitability for downstream applications such as drug design and CRISPR-based targeting.In this study, we present an integrated structural and network-based characterization of human ABL1 using the crystal structure PDB ID: 8I7S. By combining structural validation, conformational analysis, protein–protein interaction mapping, and sequence-motif annotation, we aim to establish the structural reliability, functional integrity, and regulatory significance of ABL1 in the context of myeloid leukemia, thereby providing a robust framework for structure-guided therapeutic and gene-editing strategies (kumari et al.,2025) Biopython Supported pipeline for motif detection,active site validation and interaction network validated across the reproducibility (kumari et al 2023-2025)

II.Materials and Methods

1. Protein Structure Retrieval and Preparation

The three-dimensional structure of human ABL1 kinase domain was retrieved from the Protein Data Bank (PDB)**.** The crystal structure PDB ID: 8I7S, corresponding to the ABL1 kinase domain (chain A; 272 amino acids), was selected as the primary structural model for analysis. Additional ABL1-related structures **(**PDB IDs: 7W7Y and 6XR6**)** were used for comparative structural analysis.Protein structures were visualized and analyzed using PyMOL (Schrödinger, LLC)**.** Prior to analysis, heteroatoms, solvent molecules, and non-essential ligands were removed where necessary to ensure uniformity during structural superposition and RMSD calculations.

2. Structural Superposition and RMSD Analysis

Structural similarity between ABL1 structures (8I7S vs 7W7Y and 8I7S vs 6XR6) was assessed through Root Mean Square Deviation (RMSD) calculations. Structures were superimposed using backbone Cα atoms in PyMOL to minimize positional differences.

RMSD values were interpreted according to standard structural biology thresholds:

- 0.0–1.0 Å: excellent structural alignment
- 1.0–2.0 Å: good alignment indicating high structural similarity

This analysis was used to evaluate conformational consistency, reliability of the structural model, and suitability for downstream structural and drug-design studies.

3. Structure Validation and Quality Assessment

Structural quality of the ABL1 protein (8I7S) was assessed using structure validation tools, including error-value analysis and Ramachandran plot evaluation. Error distribution across residues was examined to identify regions of high structural deviation or flexibility.Ramachandran plots were generated to analyze backbone dihedral angles (φ and ψ) of amino acid residues. Residues were categorized into most favoured, allowed, and disallowed regions to determine overall stereochemical quality and structural reliability.

4. Protein–Protein Interaction Network Analysis

Protein–protein interaction (PPI) analysis was performed using the STRING database (Search Tool for the Retrieval of Interacting Genes/Proteins)**.** ABL1 was used as the query protein, and interaction networks were generated based on experimentally validated and predicted associations.STRING interaction evidence included:Curated database interactions,Experimentally determined interactions,Text mining,Co-expression analysis,Protein homology

Edges in the network represent functional associations, indicating proteins that jointly contribute to shared biological processes rather than necessarily direct physical binding. Network connectivity and interaction partners were analyzed to assess ABL1's role as a central signalling hub in leukemia-related pathways.

5. Sequence Retrieval and Similarity Analysis

The amino acid sequence of ABL1 (chain A of 8I7S) was extracted from the PDB and used for sequence-based analysis. BLASTp (Basic Local Alignment Search Tool for proteins) was employed to identify homologous sequences and evaluate evolutionary conservation.Sequence alignments were interpreted using standard BLAST metrics, including percentage identity, query coverage, and E-values. Conserved regions were correlated with known functional and catalytic domains.

6. Motif and Domain Annotation

Functional motif identification was performed using the PROSITE database**.** Pattern-based motif searches were conducted to identify conserved kinase motifs, including:

- ATP-binding glycine-rich loop (LGGGQYG)
- Catalytic HRD motif
- DFG motif within the activation loop

Domain architecture was further analyzed using protein family and domain classification tools to identify:

- Protein kinase domain
- Tyrosine-protein kinase catalytic (PTKc) domain
- STYKc (Ser/Thr/Tyr kinase catalytic) domain

Ruler-based visualizations were used to map motifs, domains, and active sites along the 272-amino-acid sequence.

7. Active Site and Binding Site Identification

Active site residues, including catalytic aspartate (proton acceptor) and ATP-binding residues, were identified through sequence motif analysis and structural mapping. Predicted binding sites for ATP**,** Mg^{2+} ions, and substrate polypeptides were annotated based on conserved kinase signatures and structural alignment with known kinase templates.

8. Computational Tools and Libraries

Comparable workflows integrating Biopython, NGS analysis, molecular docking, and network pharmacology have been successfully applied to leukemia, lung cancer, brain tumors, and viral oncogenic targets (Kumari et al., 2023–2025).

III.RESULTS

1. **Structural Visualization and Active Site Mapping of Human ABL1**

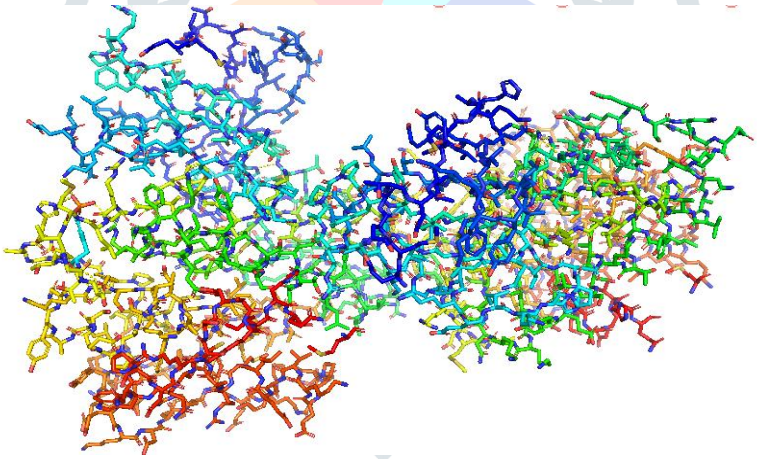

Figure 1: active site identification for chain A and chain B

The three-dimensional crystal structure of the human ABL1 kinase domain (PDB ID: 8I7S) was successfully visualized using RasMol to examine its overall folding and functional architecture. The structure exhibited the characteristic bilobed kinase organization, with a clearly defined ATP-binding cleft positioned between the N-terminal and C-terminal lobes**.** Active site residues were identified based on their spatial clustering and localization within the catalytic pocket. RasMol-based analysis enabled precise mapping of these residues, confirming the structural integrity of the kinase active site required for enzymatic function.

2. Hydrogen Bond Network Analysis and Structural Stability

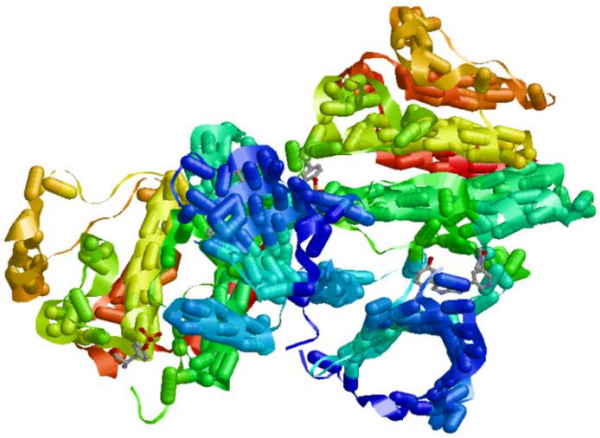

Figure2: H-bond calculation in pymol with 333 number of hydrogen bond on in myloid leukimea

Hydrogen bond interactions within the ABL1 kinase domain were analyzed using PyMOL to evaluate intramolecular stabilization. A total of 333 hydrogen bonds were identified throughout the structure, indicating a highly interconnected interaction network. A significant concentration of hydrogen bonds was observed in the active site region, hinge segment, and surrounding secondary structural elements**,** suggesting enhanced stabilization of catalytically and structurally critical regions. This extensive hydrogen bonding contributes to the maintenance of the active conformation of the ABL1 kinase domain.

3. Protein–Protein Interaction Network Analysis of ABL1

The identification of ABL1 as a central signaling hub aligns with prior network-based cancer studies demonstrating similar hub-protein behavior using STRING and Biopython (Kumari et al., 2024; Kumari et al., 2025).

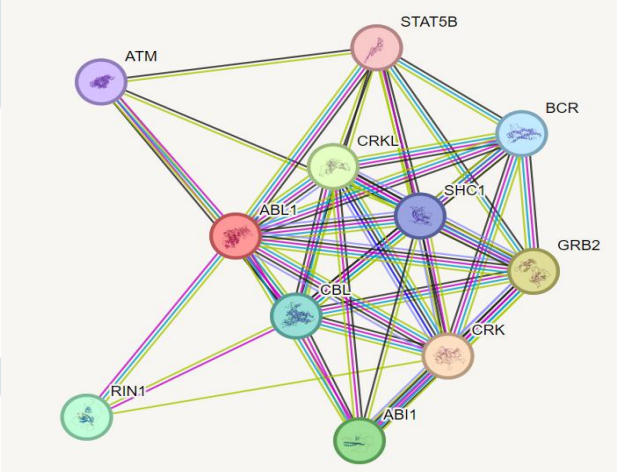

Figure 3: Protein-protein enrichment network analysis proteomic

String analysis represent the known interaction:

from curated database

experimentally determined

String analysis represent others:

Textmining

Co-expression

Protein homology

Protein–protein interaction (PPI) analysis was performed using the STRING database to investigate the functional interaction network associated with human ABL1. The generated enrichment network revealed a highly interconnected interaction map, indicating that ABL1 functions as a central signalling node within multiple cellular pathways. In the STRING network, edges represent functional protein–protein associations, where interactions denote shared biological functions rather than direct physical binding (Kumari et al 2025) The STRING analysis integrated multiple evidence channels to predict interactions. High-confidence interactions were supported by curated database annotations and experimentally determined evidence, while additional associations were inferred through text mining, co-expression patterns, and protein homology. The convergence of multiple evidence sources strengthened the reliability of the predicted interaction network.

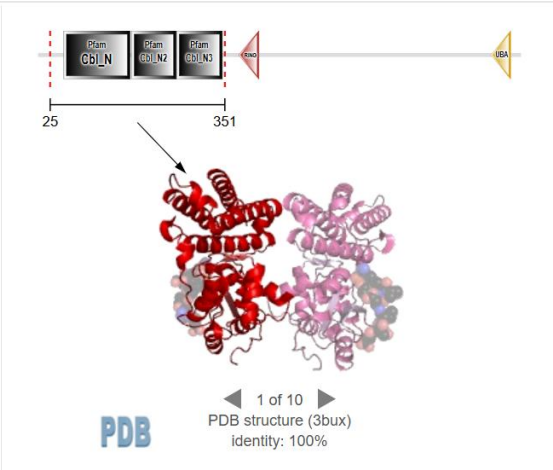

Figure 4: Protein-Protein Interaction Network

Among the predicted interaction partners, E3 ubiquitin-protein ligase CBL (ENSP00000264033) emerged as a significant regulatory component within the ABL1 network. CBL functions as a negative regulator of receptor tyrosine kinase signalling by mediating ubiquitination and proteasomal degradation of activated kinases. Its association with ABL1 highlights an important regulatory axis involved in signal termination and cellular homeostasis.

4. Functional Partner Prediction Based on Interaction Scores

Your Input:

		Neighborhood	Gene Fusion	Cooccurrence	Coexpression	Experiments	Databases	Textmining	[Homology]	Score
ABL1	*Tyrosine-protein kinase ABL1; Non-receptor tyrosine-protein kinase that plays a role in many key processes linked to cell growth and survival such as cytoskeleton remodeling in response to extracellular stimuli, cell motility and adhesion, receptor endocytosis, autophagy, DNA damage response and apoptosis. Coordinates actin remodeling through tyrosine phosphorylation of proteins controlling cytoskeleton dynamics like WASF3 (involved in branch formation); ANXA1 (involved in membrane anchoring); DBN1, DBNL, CTTN, RAPH1 and ENAH (involved in signaling); or MAPT and PXN (microtubule-bindin [...] (1149 aa)*									

Predicted Functional Partners:

CRK	*Adapter molecule crk; [Isoform Crk-II]: Regulates cell adhesion, spreading and migration. Mediates attachment-induced MAPK8...*					●	●	●	●	0.999
GRB2	*Growth factor receptor-bound protein 2; Adapter protein that provides a critical link between cell surface growth factor receptor...*					●	●	●	●	0.999
CRKL	*Crk-like protein; May mediate the transduction of intracellular signals.*					●	●	●	●	0.998
ABI1	*Abl interactor 1; May act in negative regulation of cell growth and transformation by interacting with nonreceptor tyrosine kinas...*					●	●	●		0.998
RIN1	*Ras and Rab interactor 1; Ras effector protein, which may serve as an inhibitory modulator of neuronal plasticity in aversive me...*					●	●	●		0.997
CBL	*E3 ubiquitin-protein ligase CBL; Adapter protein that functions as a negative regulator of many signaling pathways that are trig...*					●	●	●		0.996
BCR	*Breakpoint cluster region protein; Protein with a unique structure having two opposing regulatory activities toward small GTP-bi...*					●	●	●		0.996
SHC1	*SHC-transforming protein 1; Signaling adapter that couples activated growth factor receptors to signaling pathways. Participat...*					●	●	●	●	0.991
ATM	*Serine-protein kinase ATM; Serine/threonine protein kinase which activates checkpoint signaling upon double strand breaks (D...*					●	●	●		0.988
STAT5B	*Signal transducer and activator of transcription 5B; Carries out a dual function: signal transduction and activation of transcripti...*					●	●	●		0.983

Figure 5: Predicted functional partners on the basis of score (showing highest interactions)

STRING-based confidence scoring identified several high-confidence functional partners of ABL1. The highest interaction score (0.999) was observed for CRK, GRB2, and CRKL**,** indicating strong functional associations with ABL1. Additional strong interactions (score >0.99) were observed with CBL, further supporting its regulatory role within the ABL1 signalling network.
Functional classification of ABL1-associated proteins revealed distinct biological roles within the interaction network. Adaptor proteins such as CRK, GRB2, CRKL, and SHC1 were prominently represented, indicating their involvement in intracellular signal transduction. Regulatory proteins, including ABL1, CBL, and RIN1, were associated with control of cell growth, transformation, and signalling modulation. Additionally, checkpoint and DNA damage–related proteins**,** such as ATM and STAT5B, linked ABL1 to cell cycle regulation and transcriptional control. The presence of the oncogenic protein BCR further emphasizes the relevance of this network to BCR–ABL–mediated leukemogenesis.

5. Sequence Similarity and Homology Analysis

BLASTp sequence similarity analysis of the proteomic sample 8I7S, corresponding to the human ABL1 kinase domain, revealed multiple homologous tyrosine kinase sequences with very high sequence similarity. All significant hits showed near-maximum alignment scores, 100% query coverage**,** and E-values of 0.0**,** indicating highly reliable and biologically meaningful matches.The identified homologs exhibited 99.6–100% sequence identity with the query protein, confirming that the analyzed structure represents a highly conserved ABL1 kinase domain. Conservation was particularly prominent within the ATP-binding region and catalytic motifs**,** highlighting their essential role in kinase activity and signal transduction. These results demonstrate strong evolutionary conservation of ABL1 across related structures and validate the use of PDB ID 8I7S as a representative model for structural and functional studies in leukemia.

6. B-Factor Analysis and Identification of Flexible Regions in ABL1

B-factor analysis was performed to assess residue-level flexibility and dynamic behaviour of the ABL1 kinase domain in the proteomic sample associated with **myeloid leukemia**. The B-factor profile, plotted against residue position, revealed distinct regions of elevated atomic displacement, indicative of structural flexibility and potential disorder.

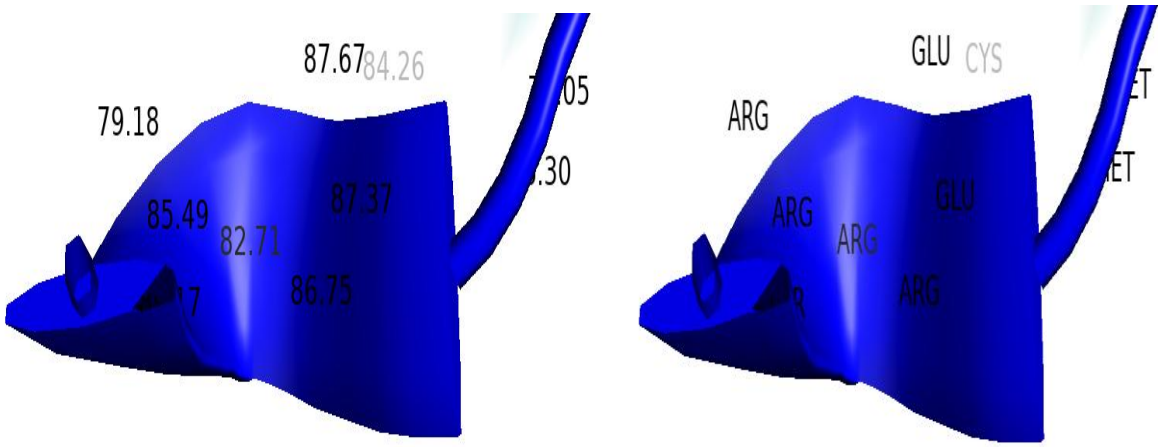

Figure 6 :B-factor analysis representing score and residue position to disordered region identification of proteomic sample myeloid Leukemia.

Residues exhibiting high B-factor values, including ARG (85.49) and GLU (87.67)**,** were primarily localized to loop regions and surface-exposed segments of the protein. These regions are typically associated with increased conformational mobility and are often involved in regulatory control and protein–protein interactions. The observed flexibility suggests functional relevance in kinase regulation and signal modulation.Additional high B-factor residues, such as GLN (81.73)**,** were identified within regions proximal to the active and regulatory sites of ABL1. These residues correspond to flexible structural elements that may facilitate substrate accessibility, conformational transitions, and interaction with regulatory partners. The presence of dynamic regions near functional sites highlights their potential role in ABL1 activation and signalling.

7. Active Site Validation and Structural Alignment Analysis

To validate the structural reliability and active-site conservation of the ABL1 kinase domain, root mean square deviation (RMSD) analysis was performed using PyMOL. Structural alignment of PDB ID: 8I7S with reference kinase structures enabled quantitative assessment of conformational similarity and binding-site preservation.

8.RMSD Analysis of 8I7S and 7W7Y

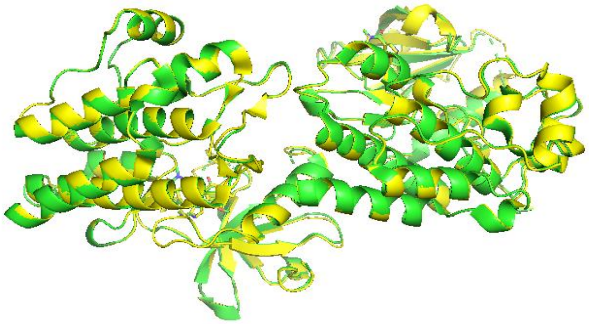

Figure 7: RMSD calculation for 8i7S (green) 7w7y (yellow) with 0.2 Angstrom

Alignment of 8I7S with 7W7Y resulted in the alignment of 4,229 atoms, with 3,469 atom pairs contributing to the RMSD calculation. The resulting RMSD value of 0.247 Å indicates an excellent structural alignment, reflecting near-identical backbone and active-site conformations. Such a low RMSD value confirms strong conservation of the ABL1 kinase fold and validates the accuracy of the modelled active-site geometry.Further structural comparison of 8I7S with 6XR6 yielded an RMSD value of 1.2 Å**,** indicating good structural alignment with minor deviations. This level of RMSD is characteristic of homologous protein structures or conserved binding conformations and suggests that the overall architecture and active-site orientation remain highly similar between the compared structures.RMSD-based structural conservation and Ramachandran plot validation observed here are comparable to previous structure-guided cancer and leukemia studies employing similar computational validation pipelines (Kumari et al., 2024; Kumari et al., 2025).The RMSD analyses demonstrate that 8I7S maintains high structural fidelity when compared with reference ABL1-related structures. The excellent alignment with 7W7Y and strong similarity with 6XR6 indicates that the active-site configuration is conserved and reliable**,** supporting the suitability of the 8I7S structure for structure-guided drug design, docking studies, and functional analyses in the context of leukemia.

9.**Structure Validation Analysis of the ABL1 Kinase Domain**

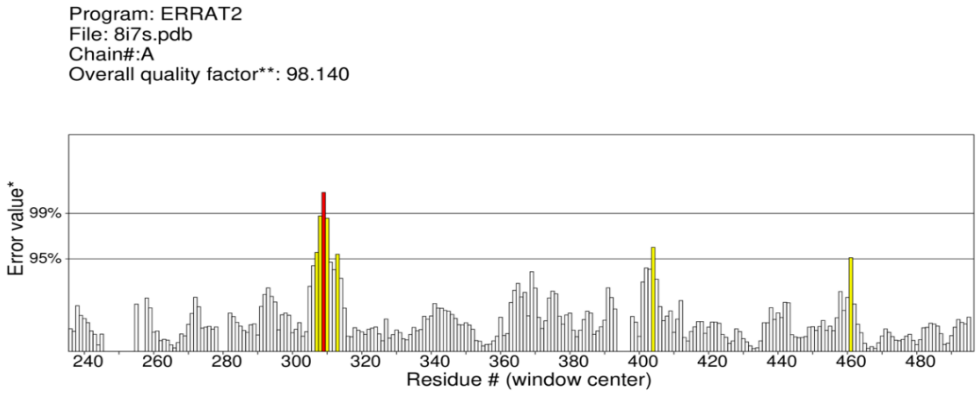

Figure 8: Structure Validation analysis in proteomic sample (8i7s)

structure validation of the ABL1 proteomic sample **(**PDB ID: 8I7S**)** was performed to assess the reliability and quality of the modelled protein structure. The validation analysis yielded an overall quality score of 98.1405, indicating a high level of structural accuracy and consistency.

Ramachandran Plot Analysis Using BioPython

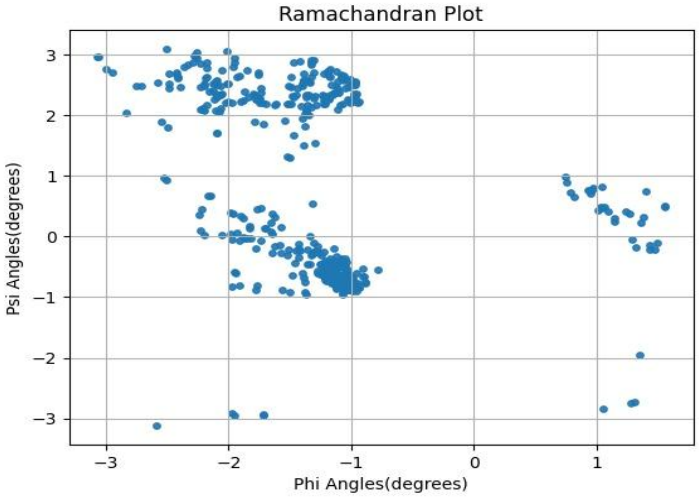

Figure 9: Ramachandran plot

The conformational quality of the ABL1 kinase domain structure was evaluated using a Ramachandran plot generated through BioPython, which analyses the backbone torsional angles ϕ (phi) and ψ (psi) of individual amino acid residues. The plot displays phi angles on the X-axis and psi angles on the Y-axis, providing insight into the stereochemical feasibility of residue conformations within the protein backbone.

The majority of residues were observed to cluster within the most favoured regions, corresponding to energetically stable conformations typically associated with α-helices and β-sheet structures. A smaller number of residues occupied the additionally allowed regions, which represent acceptable but less energetically favourable conformations. Only a minimal number of residues appeared in the disallowed regions, indicating very limited steric clashes or unfavourable backbone geometry.The dominant localization of residues within favoured and allowed regions demonstrates that the ABL1 structure exhibits good stereochemical integrity and conformational stability**.** This distribution confirms the structural validity and reliability of the modelled protein and supports its suitability for downstream analyses, including structure validation, active-site characterization, protein–protein interaction studies, and structure-guided drug design in the context of myeloid leukemia.

10.Sequence Annotation of ABL1 Kinase Domain (PDB: 8I7S)

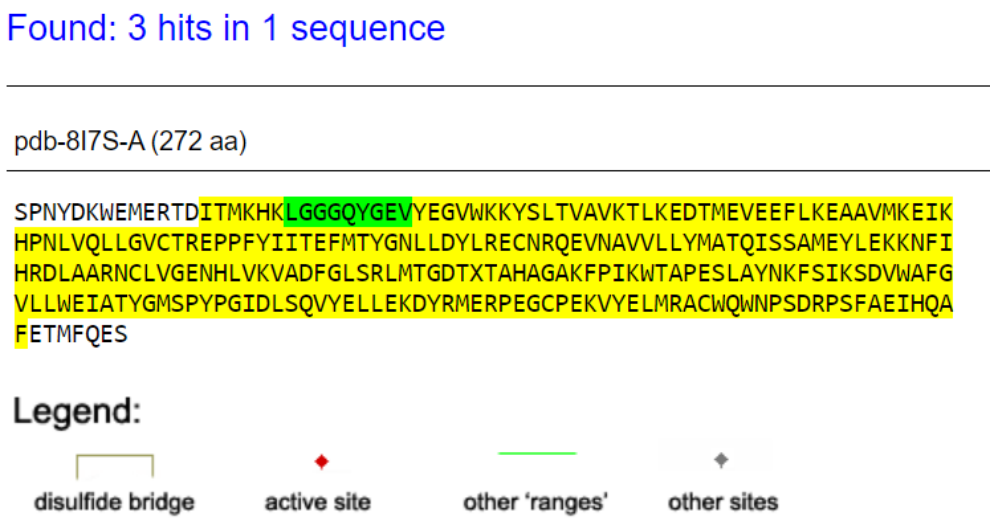

Figure 10: It represent sequence annotation result for protein chain pdb8i7s-A (272 amino acid)

Sequence annotation analysis was performed for protein chain A of PDB ID: 8I7S**,** comprising 272 amino acids**,** to identify conserved functional and structural features. The annotated sequence visualization highlighted the full-length amino acid sequence in yellow, providing a comprehensive overview of residue coverage across the chain.

A green-highlighted stretch corresponding to the conserved motif "LGGGQYGEV" was identified within the sequence. This motif is characteristic of kinase proteins and is associated with nucleotide binding and catalytic function. Additional legend annotations indicated distinct functional regions, with green underlined segments representing conserved motifs**,** while uppercase letters denoted matched positions. Overall, sequence annotation revealed the presence of three important conserved functional/structural motifs, supporting the biological activity and structural stability of the protein.

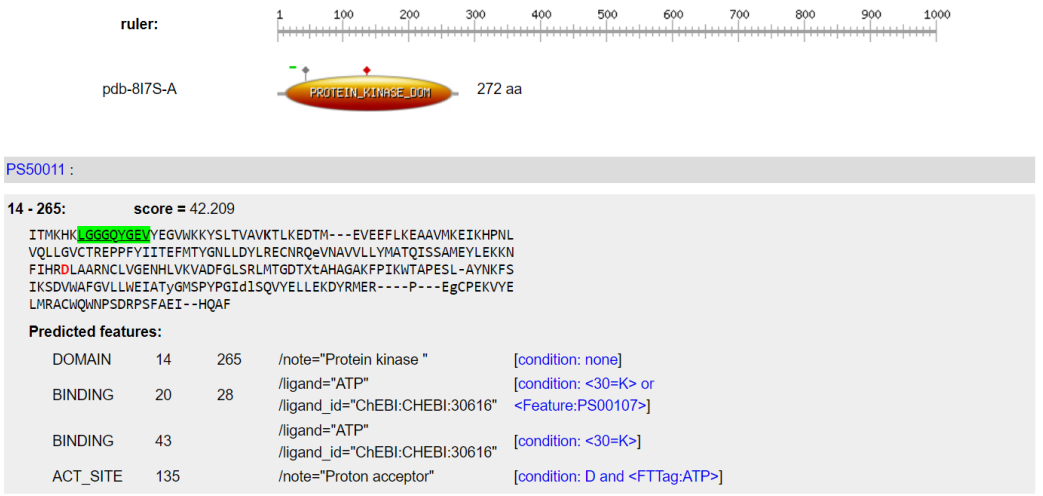

Figure 11: shows domain and motif annotation for the protein chain pdb- 8i7s-A (272 amino acid) using prosite

Domain and motif annotation using the PROSITE database (pattern PS5001) further characterized the functional organization of the protein chain. Ruler-based visualization provided a linear representation of the protein sequence length **(**0–272 residues**),** enabling precise mapping of domains, motifs, and active sites along the sequence.The protein kinase domain was identified between residues 14 and 265, represented by an orange oval on the ruler. Within this domain, ATP-binding and catalytic active sites were mapped at their respective residue positions, marked using green and red indicators. These features confirm that pdb-8i7s-A is structurally and functionally consistent with a kinase enzyme**,** possessing conserved residues essential for phosphorylation-dependent signalling and regulatory processes.

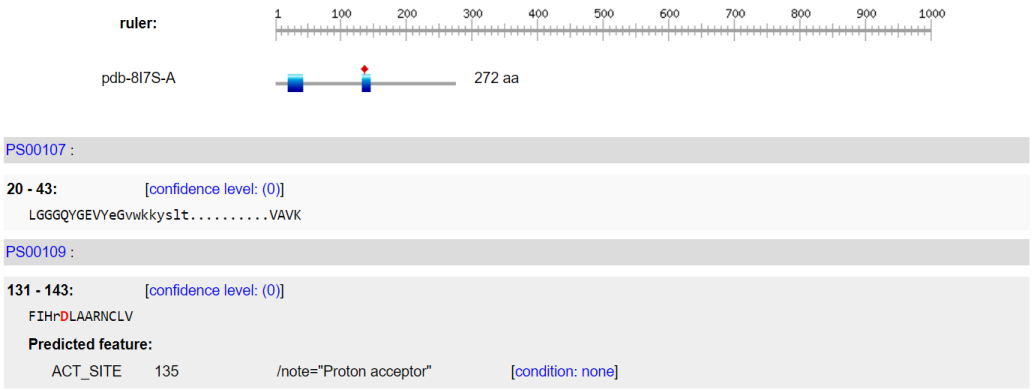

Figure 12: Pattern- based motif search results for the protein sequence 8I7S

Pattern-based motif analysis using the PROSITE database identified conserved motifs within the protein sequence. The PS00107 motif, spanning the 20–43 amino acid region, was detected with the sequence LGGGQYGvwkkyslt..yawk, corresponding to the ATP-binding motif typical of protein kinases.Additionally, the PS00109 motif was identified within the 131–143 amino acid region, with the sequence FIHrDLAARNCLV. This motif includes an aspartate residue at position 135, predicted to function as a proton acceptor, indicating a critical catalytic residue involved in enzymatic activity.The presence of conserved ATP-binding and catalytic motifs confirms that pdb-8i7s-A is functionally characterized as an enzymatically active kinase**.** These motifs support ATP-dependent catalysis and reinforce the role of ABL1 in phosphorylation-mediated signalling pathways. The conserved sequence architecture and motif composition further validate the protein's functional integrity and suitability for downstream structural, interaction, and therapeutic targeting studies.

12.Structural Bioinformatics Analysis Using Biopython

Residue-level structural parsing of the ABL1 structure using the Bio.PDB module revealed organized chain architecture with consistent residue numbering. Scatter plots mapping residue positions across chains illustrated uniform residue distribution along chain A.

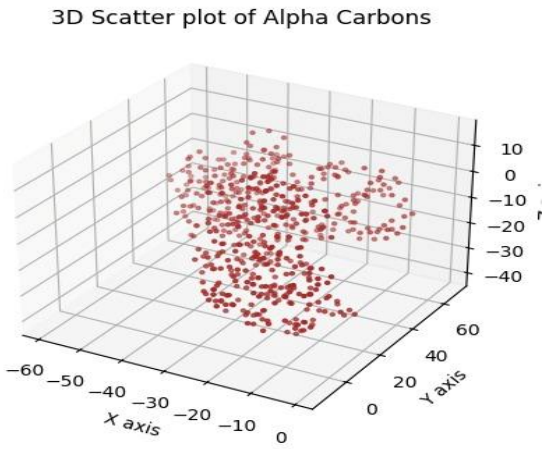

Figure 13: 3D Scatter plot of Alpha Carbons

Three-dimensional visualization of α-carbon (CA) atoms demonstrated the spatial folding and geometric organization of the kinase domain. The 3D scatter plot confirmed compact domain architecture with well-defined secondary structural elements.

13. Hydrophobicity and Sequence Feature Analysis

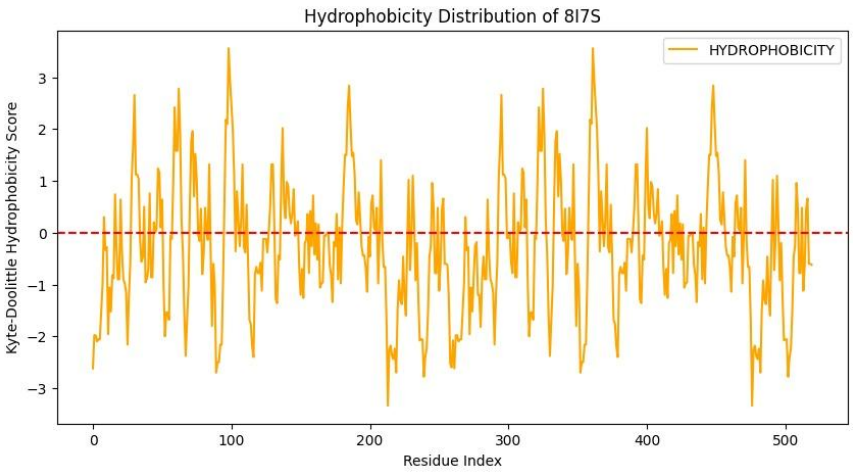

Figure 14: Hydrophobicity distribution of 8I7S

Hydrophobicity profiling based on the Kyte–Doolittle scale revealed alternating hydrophobic and hydrophilic regions along the protein sequence. Sliding-window smoothing highlighted conserved hydrophobic segments corresponding to the kinase core and substrate interaction regions, while surface-exposed regions exhibited higher hydrophilicity.The convergence of structural stability, conserved motifs, and dense interaction networks observed for ABL1 mirrors findings from earlier NGS- and Biopython-driven cancer bioinformatics investigations, reinforcing the translational relevance of this integrative approach (Kumari et al., 2023–2025)

CONCLUSION

This study establishes ABL1 as a structurally conserved and functionally central signalling hub in leukemia through an integrated structural, sequence, and protein–protein interaction network analysis. High-resolution structural evaluation of the ABL1 kinase domain confirmed a canonical tyrosine kinase fold with preserved catalytic motifs and limited conformational variability, supporting its reliability as a functional model. Localized flexibility within regulatory and activation regions highlights their importance in kinase regulation, substrate recognition, and inhibitor binding. Sequence conservation and network profiling further positioned ABL1 as a highly connected node interacting with major oncogenic signalling partners, providing a mechanistic basis for its critical role in leukemogenesis. Together, these findings demonstrate how the combination of conserved catalytic architecture, dynamic regulatory elements, and extensive network connectivity underpins ABL1-driven signalling, reinforcing its significance as a key therapeutic target in leukemia.

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