RESEARCH PAPER

NGS mutation Profiling of TP53 gene analysis in Oral Squamous Cell Carcinoma (OSCC)

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ABSTRACT

The most prevalent cancer in the oral cavity, oral squamous cell carcinoma (OSCC), is a significant public health concern, particularly for Asian populations. One of the main causes of the onset and progression of this illness is mutations in tumor suppressor genes. With mutation rates reported in 60–80% of cases, the TP53 gene is the most frequently mutated gene in OSCC. This study aimed to explore the mutational profile of the TP53 gene in OSCC using next-generation sequencing (NGS) and to evaluate the functional impact of the identified mutations with structural bioinformatics tools. The TP53 protein structure was modelled using the crystal data (PDB ID: 1TSR) from the Protein Data Bank. Mutation data were examined with multiple computational resources, including MMDB for structural annotation, InterProScan and PROSITE for identifying domains and motifs, Protein enrichment analysis for protein-protein interactions, and PDBsum and LigPlot for visualising ligand-binding sites and residue interactions. Additionally, B-factor analysis was conducted to evaluate the structural flexibility and stability of residues within TP53. NGS data showed that most TP53 mutations are located in the DNA-binding domain (DBD), mostly as missense mutations targeting critical residues involved in DNA recognition and transcriptional regulation. Structural insights from MMDB and PDBsum revealed that several mutated residues are located in highly conserved regions crucial for DNA binding and protein stability. B-factor analysis indicated increased flexibility at these mutated sites, which may destabilize the protein's structure. Additionally, protein interaction analysis identified TP53 as interacting with various regulatory proteins that control apoptosis, DNA repair, and the cell cycle. These findings emphasize the significance of combining NGS-based mutation profiling with structural bioinformatics tools to better understand the molecular mechanisms driving OSCC development. The research sheds light on how TP53 mutations compromise structural stability and regulatory interactions, which can lead to tumor formation. Integrating these methods could facilitate the discovery of potential biomarkers and therapeutic targets, advancing precision medicine in oral cancer treatment.

Keywords: TP53, Oral Squamous Cell Carcinoma, Next Generation Sequencing, Structural Bioinformatics, Protein Data Bank, Mutation Analysis, Protein Interaction Network, Cancer Genomics.

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INTRODUCTION

Approximately 90% of oral cancers worldwide are oral squamous cell carcinoma (OSCC), one of the most common cancers in the head and neck region. Its prevalence is particularly high in developing nations like India, where smoking, chewing tobacco, drinking alcohol, and consuming betel nuts all play important roles in its development.[1] Despite progress in surgical procedures, radiotherapy, and chemotherapy, the survival rates for OSCC patients have stayed relatively low over recent decades. This is mainly due to late detection, tumour heterogeneity, and the complex molecular mechanisms involved. [2]

Cancer development results from the buildup of genetic and epigenetic changes that interfere with normal cell functions like proliferation, apoptosis, DNA repair, and cell cycle control. In OSCC, many oncogenes and tumour suppressor genes are often mutated. Notably, the TP53 gene stands out as a key molecular factor in oral cancer development. TP53 codes for the tumour suppressor protein p53, known as the “guardian of the genome” due to its vital role in preserving genomic stability. p53 oversees various cellular activities, including DNA repair, cell cycle arrest, apoptosis, and senescence. [3,4] When DNA damage occurs, p53 activates and promotes the expression of genes that either fix the damage or induce programmed cell death.

Mutations in TP53 are among the most common genetic alterations in human cancers, found in over half of all malignancies. In OSCC, TP53 mutations have been

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reported in 35% to 80% of cases, underscoring its key role in disease development. These mutations frequently lead to the loss of tumor suppressor functions or the gain of oncogenic capabilities, which drive tumor growth, invasion, and therapy resistance. [5] Advances in next-generation sequencing (NGS) technologies have transformed cancer genomics by allowing high-throughput detection of genetic changes across whole genomes or specific gene panels. NGS serves as a robust tool for identifying single nucleotide variants, insertions, deletions, and structural rearrangements linked to cancer. In OSCC, NGS research has uncovered numerous recurrent mutations in genes like TP53, NOTCH1, CDKN2A, HRAS, and PIK3CA, which play crucial roles in signalling pathways that control cell growth and survival. [6,7]

TP53 mutations are especially important among these genes because they tend to happen early in tumour development and affect how the tumour behaves, its prognosis, and its response to therapy. Many of these mutations occur within the DNA-binding domain (DBD), a highly conserved area vital for recognizing specific DNA sequences and activating the transcription of downstream genes. Mutations in this domain can impair DNA binding, resulting in disrupted transcriptional regulation and loss of tumour suppressor activity.[8] While genomic studies have effectively pinpointed mutation patterns, comprehending how these mutations impact protein structure and function demand further computational and structural analysis. Structural bioinformatics tools offer important insights into how amino acid substitutions can alter protein folding, stability, and interactions with other molecules. Combining genomic data with structural approaches can therefore improve our understanding of mutations linked to cancer.[9] The Protein Data Bank (PDB) offers experimentally determined three-dimensional structures of proteins and macromolecules, useful for analysing mutation effects on structure. In this study, the crystal structure of the TP53 DNA-binding domain (PDB ID: 1TSR) served as the template for analysis. We also employed various databases and tools, including Molecular Modelling Database (MMDB), InterProScan, PROSITE, STRING, PDBsum, and LigPlot, to examine protein domains, motifs, interaction networks, and ligand-binding interactions. [11,12] Additionally, examining B-factors (temperature factors) in protein structures offers valuable insights into atomic movement and flexibility. Residues exhibiting higher B-factor values typically indicate flexible or unstable areas, making them more vulnerable to functional disruptions when mutated.[13]

Integrating NGS mutation data with structural bioinformatics provides a comprehensive framework to understand the functional effects of TP53 mutations in OSCC. By pinpointing key residues and interaction networks impacted by these mutations, researchers can gain deeper insights into tumor biology and identify promising therapeutic targets.[14] This study aims to analyze the mutational landscape of TP53 in OSCC using NGS data and to explore the structural and functional impacts of these mutations through computational structural biology methods.[15]

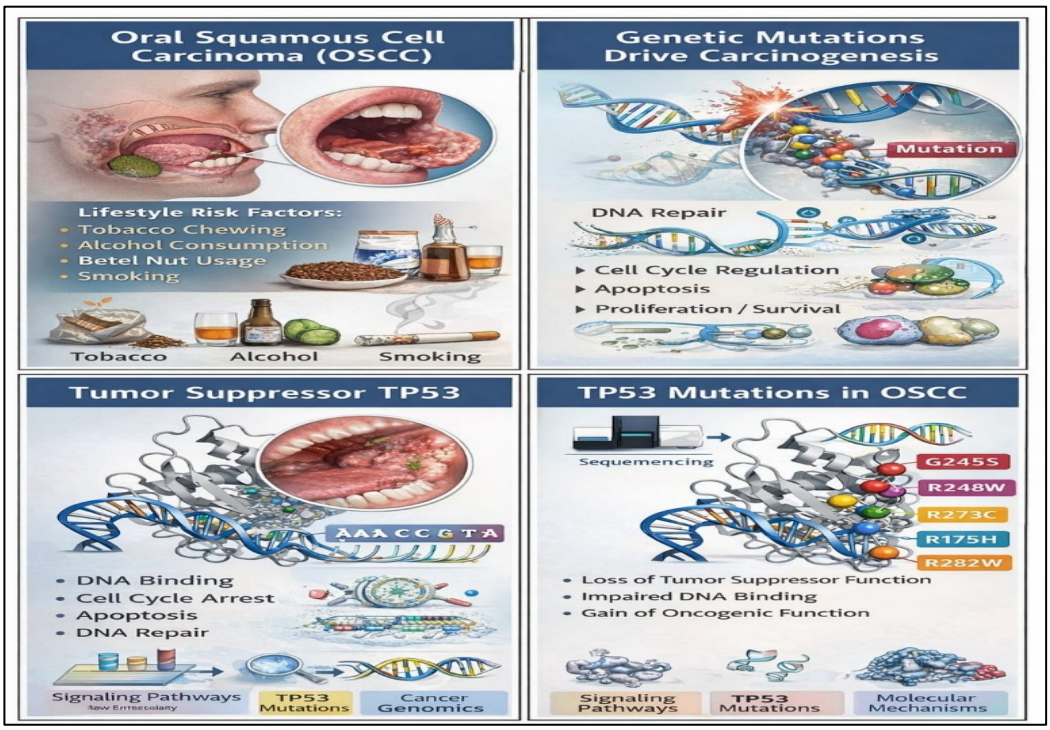

Figure 1: Oral Cancer, Gene mutation, Tumour suppressor gene TP53 Analysis

METHADOLOGY

1. Data Collection and Sequence Retrieval

The TP53 protein sequence and structural information were sourced from publicly accessible biological databases. The 3D crystal structure of the TP53 DNA-binding domain was retrieved from the Protein Data Bank (PDB) under ID 1TSR. This structure depicts the core region of human p53, which is essential for DNA recognition and transcriptional control.

2. Analysis of Next Generation Sequencing Data

NGS data on oral squamous cell carcinoma were sourced from publicly accessible genomic databases and literature reports. Variant calling and mutation annotation followed standard genomic procedures. The TP53 mutations identified were classified into various categories, including:

- Missense mutations
- Nonsense mutations
- Frameshift mutations
- Splice site mutations

The analysis of mutation frequency and distribution across different protein domains aimed to pinpoint hotspot regions within the TP53 protein.

3. Structural Annotation using MMDB

The Molecular Modelling Database (MMDB) was utilized to examine the structural organization of the TP53 protein. It offers details on secondary structures, domain arrangements, and residue-specific features. These structural annotations facilitated the identification of residues crucial for DNA binding, zinc coordination, and maintaining protein stability.

4. Domain and motif recognition

Protein domain and motif analysis was conducted with InterProScan and PROSITE databases to identify conserved functional regions within the TP53 protein, including:

- Transactivation domain
- Proline-rich region
- DNA-binding domain
- Oligomerization domain

Conserved motifs involved in DNA interaction and transcriptional activation were also identified.

5. Protein-Protein Interaction Network Analysis

Protein interaction analysis was performed using the STRING database, combining experimental and predicted data. The TP53 protein interaction network was built to identify major interacting partners involved in cellular pathways such as:

- DNA repair
- Apoptosis
- Cell cycle regulation
- Signal transduction

The interaction network highlighted TP53's key role in controlling various cellular functions.

6. Structural Interaction Analysis using PDBsum and LigPlot

Structural interaction analysis was performed using PDBsum and LigPlot, which offer visual representations of protein-ligand and protein-DNA interactions. Residues involved in hydrogen bonds, hydrophobic contacts, and metal coordination were identified and mapped onto the TP53 structure. This helped determine if mutation sites overlapped with functional regions.

7. B-Factor Analysis

B-factor analysis was conducted using the structural coordinates from the PDB structure. These B-factor values indicate atomic displacement or flexibility within the protein. Areas with higher B-factor values were identified as flexible or unstable regions. Mutation sites were mapped onto the structure to determine if they are located within these highly flexible regions.[16]

8. Structural Visualization

Protein structures and mutation sites were visualized using molecular visualization tools like PyMOL. Structural mapping enabled the identification of mutation hotspots within the three-dimensional structure of the TP53 protein.[17]

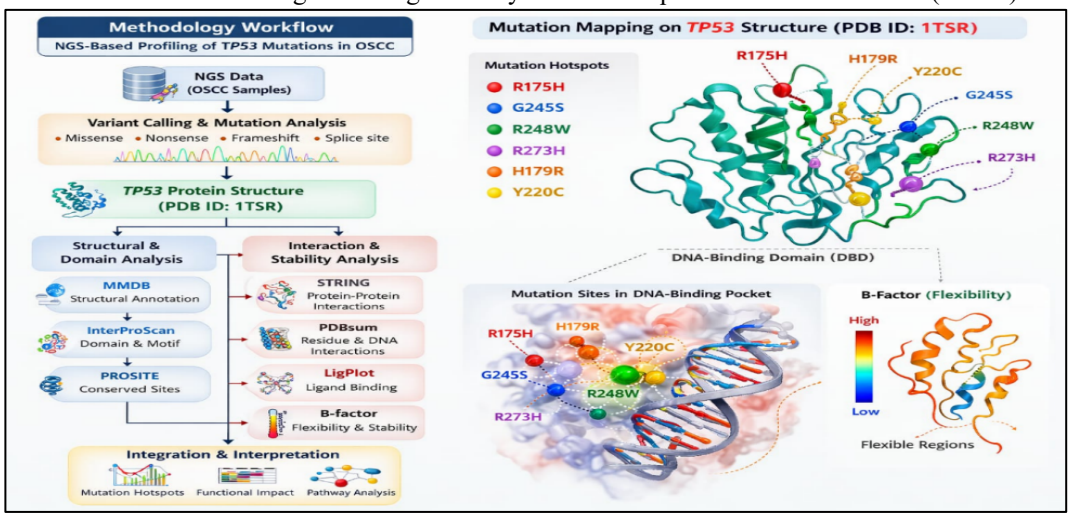

Figure 2: Working Pipeline and mutation mapping of the sample 1TSR

RESULT

1TSR | pdb_00001tsr

P53 CORE DOMAIN IN COMPLEX WITH DNA

- Classification: ANTITUMOR PROTEIN/DNA
- Organism(s): Homo sapiens
- Mutation(s): sequence mutation

MMDB DATABASE

Chain A, PROTEIN (P53 TUMOR SUPPRESSOR)

PDB: 1TSR_A

>pdb|1TSR|A Chain A, PROTEIN (P53 TUMOR SUPPRESSOR)

SSSVPSQKTYQGSYGFRLGFLHSGTAKSVTCTYS
PALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAM
AIYKQSQHMTEVVRRCPHHERCSDSDGLAPPQH
LIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGS
DCTTIHYNYMCNSSCMGGMNRRPILTIITLEDSSG
NLLGRNSFEVRVCACPGRDRRTEEENLRKKGEPH
HELPPGSTKRALPNNT

ERRAT

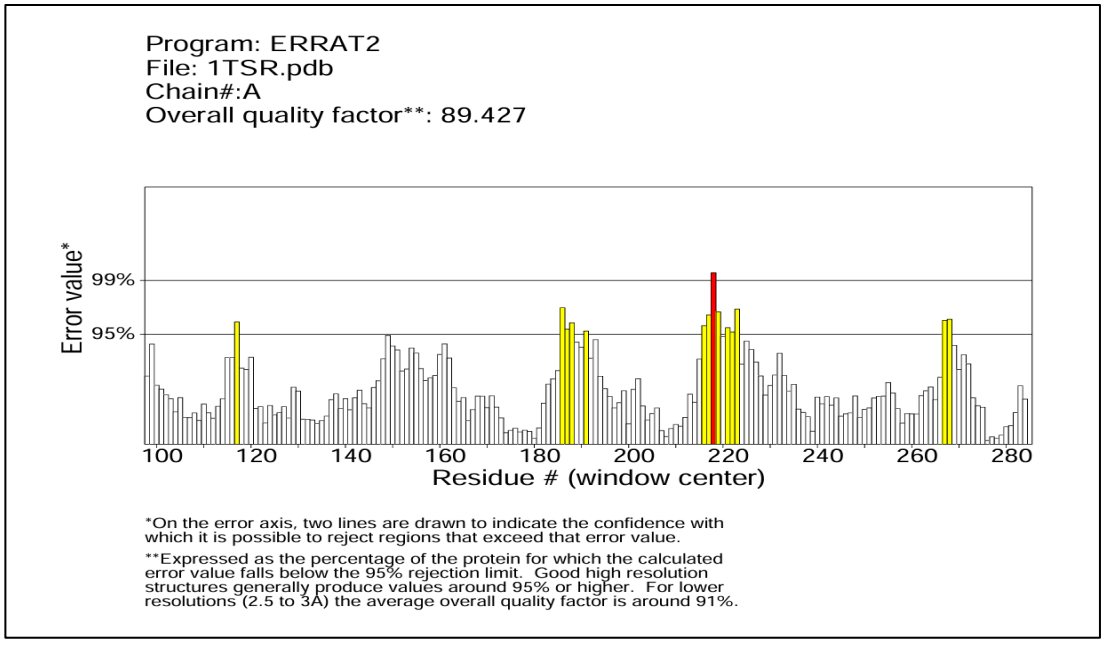

Figure 3: Structure validation Analysis of the sample P53 Core domain in complex with DNA is 89.72%

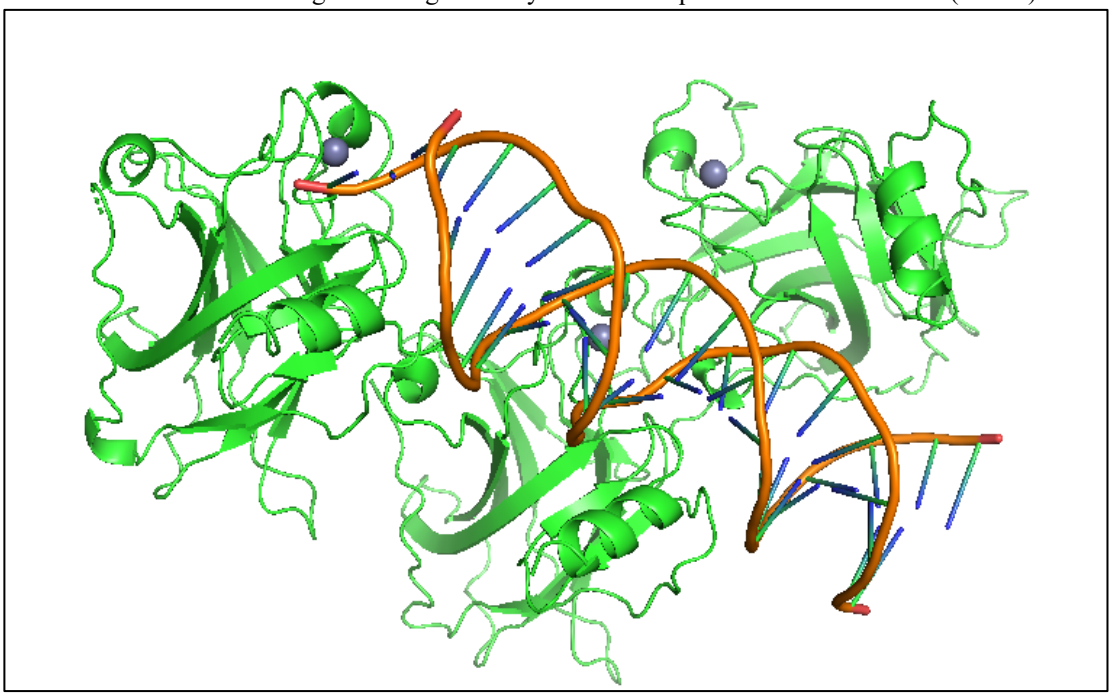

Figure 4: Structure of sample protein antitumor protein P53 Core domain

Interproscan Analysis

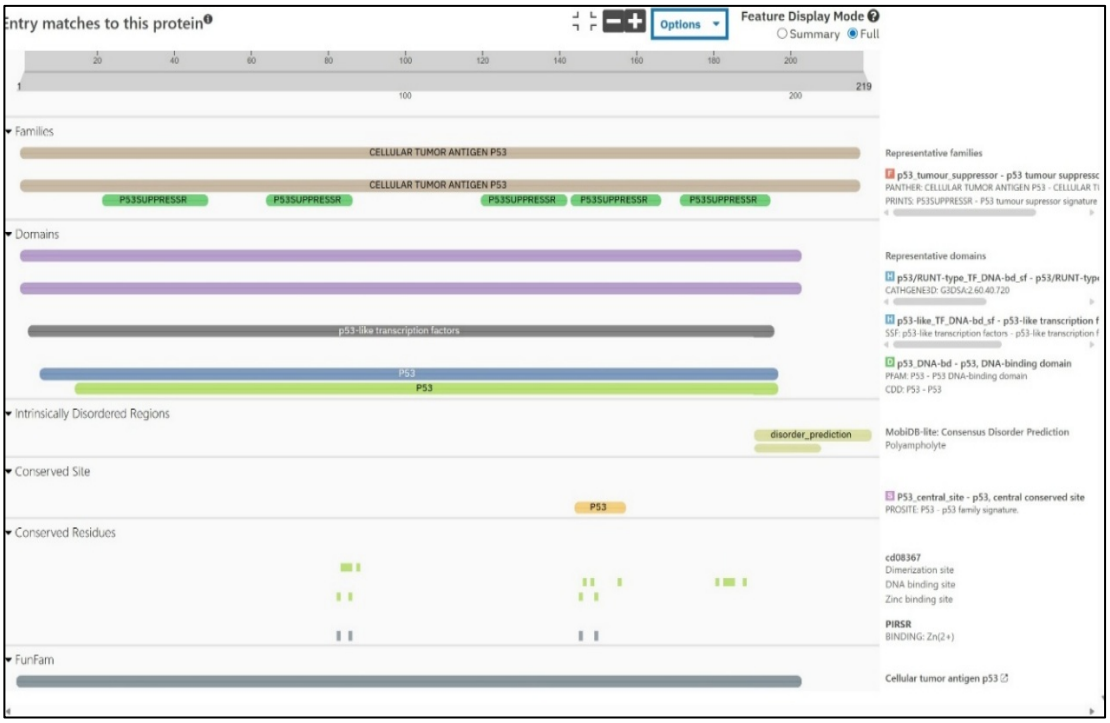

Figure 5: Protein signature analysis of antitumor protein

The InterProScan analysis of the 219-amino acid p53 protein highlights its classification as a cellular tumor antigen within the P53SUPPRESSR family, emphasizing its key role as a tumour suppressor. The protein structure features a clear DNA-binding domain (p53_DNA-bd), supported by annotations from PFAM, CDD, and PROSITE, along with broader structural categories like p53-like transcription factors and the RUNT-type_TF_DNA-bd superfamily. These domains enable p53 to regulate transcriptional responses to DNA damage and stress effectively. The sequence includes conserved residues and motifs, such as zinc-binding sites and dimerization interfaces, essential for structural stability and tetramer formation. MobidDB-lite disorder

prediction reveals intrinsically disordered, polyampholyte regions, indicating flexibility that promotes dynamic protein-protein interactions and regulatory functions. Functional motifs like DNA-binding and Zn^{2+} coordination sites further support p53's role in maintaining genomic integrity. Collectively, these details depict p53 as a structurally modular yet functionally robust protein, combining ordered domains with disordered regions to carry out its critical functions in cell cycle regulation, apoptosis, and tumor suppression.

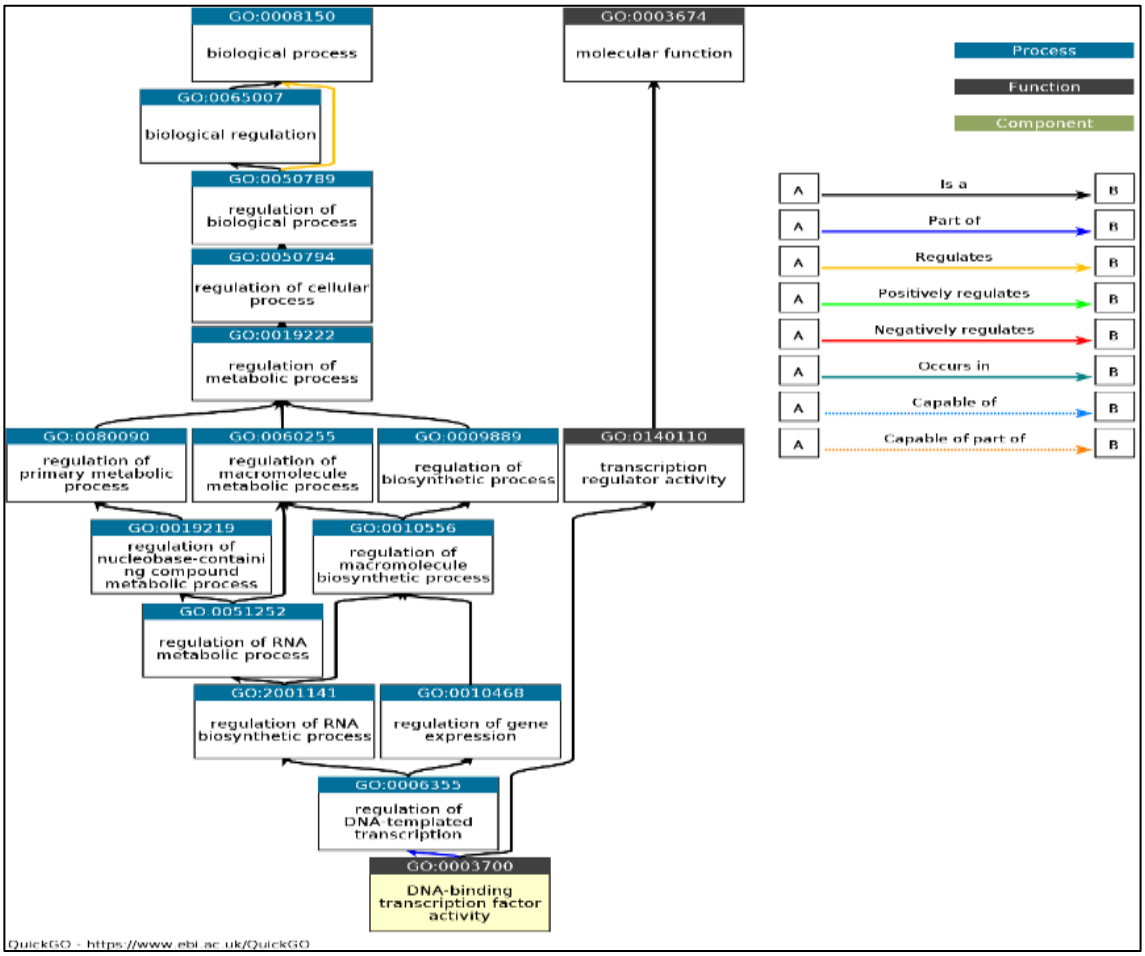

Figure 6: DNA-binding transcription factor activity

The diagram shows how Gene Ontology (GO) categorizes regulatory processes and transcriptional control within a hierarchical structure. At the highest level, biological processes include biological regulation, which narrows down to cellular and metabolic regulation, eventually focusing on gene expression and transcription. In this sequence, transcriptional regulation involves two roles: transcription coregulators, which influence activity without binding DNA directly, and DNA-binding transcription factors, which interact with genetic material to regulate transcription. The molecular function branch emphasizes this duality by classifying transcription factors both as functional molecules and as components of biological regulation. This positioning underscores their central importance in both mechanistic and functional aspects. Overall, the diagram highlights the nested organization of regulation, the difference between coregulators and transcription factors, and the vital role of transcription factors as both molecular functions and as regulators of biological processes, making them key points for annotation, pathway analysis, and translational research.

PROSITE

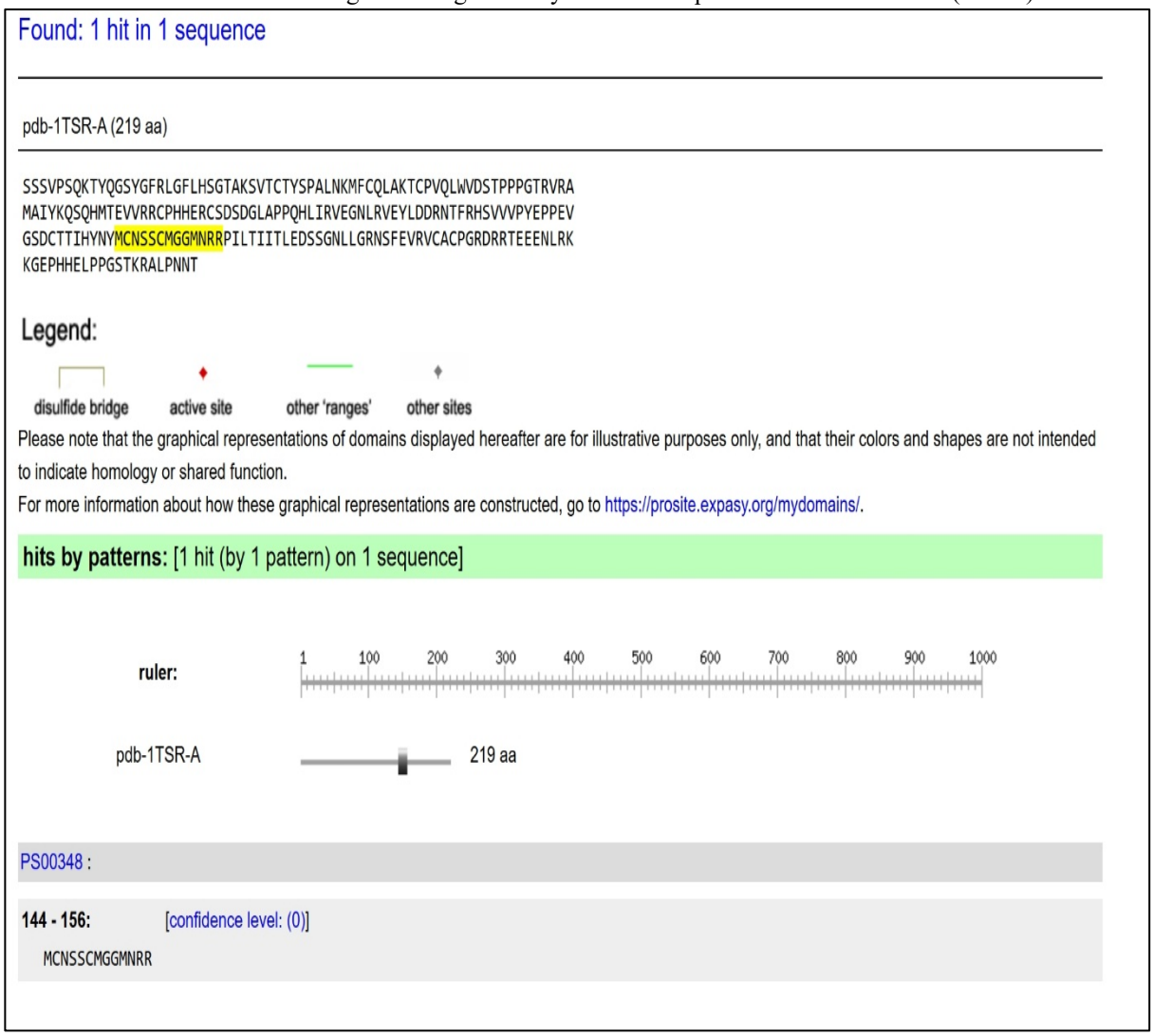

Figure 7: Conserved site analysis of sample antitumor protein with PROSITE

The PROSITE analysis of the protein sequence pdb-1TSR-A (219 amino acids) identifies a single match to the motif PS00348 between residues 144–156, corresponding to the sequence HCNSCSGMRRRR. This motif includes multiple cysteine and histidine residues, often linked to structural features such as disulfide bridges or metal-binding sites, as well as a stretch of arginine's that may facilitate nucleic acid binding or protein–protein interactions. However, the confidence level for this match is reported as 0, suggesting that the alignment is weak and should be interpreted with caution, as it may represent a degenerate or non-functional version of the canonical motif. Although the presence of cysteine- and arginine-rich regions suggests potential structural or regulatory roles, experimental validation is necessary to confirm whether this site indeed performs the function associated with PS00348. Overall, the result indicates a tentative annotation of a possible functional site, but its biological significance remains uncertain without further supporting evidence.

Protein -Protein Interaction Network Analysis

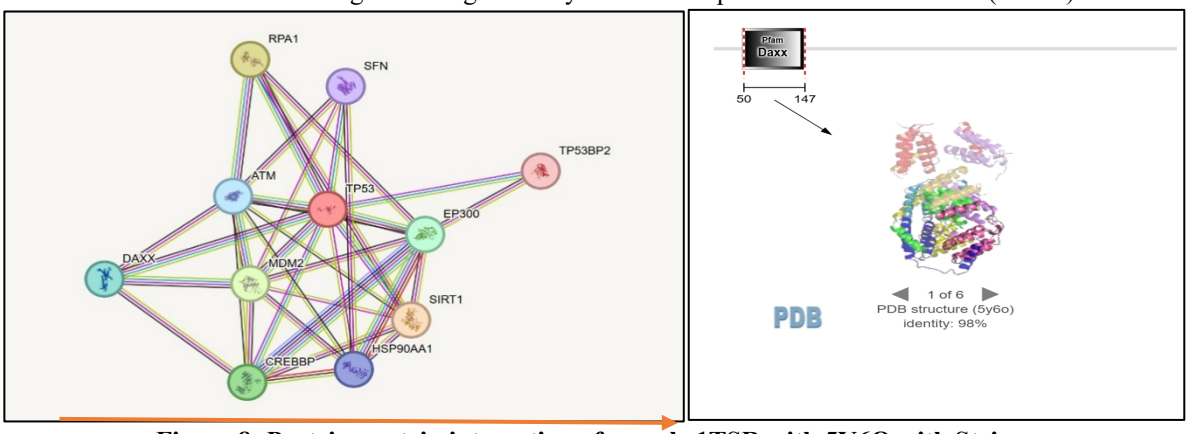

Figure 8: Protein-protein interaction of sample 1TSR with 5Y6O with String

Network Stats

number of nodes:	11	expected number of edges:	26
number of edges:	35	PPI enrichment p-value:	0.0582
average node degree:	6.36		
avg. local clustering coefficient:	0.838		

*your network does **not** have significantly more interactions than expected (what does that mean?)*

Your Input:

		Neighborhood	Gene Fusion	Cooccurrence	Coexpression	Experiments	Databases	Textmining	[Homology]	Score
TP53	Cellular tumor antigen p53; Acts as a tumor suppressor in many tumor types; induces growth arrest or apoptosis depending on the physiological circumstances and cell type. Involved in cell cycle regulation as a trans-activator that acts to negatively regulate cell division by controlling a set of genes required for this process. One of the activated genes is an inhibitor of cyclin-dependent kinases. Apoptosis induction seems to be mediated either by stimulation of BAX and FAS antigen expression, or by repression of Bcl-2 expression. Its pro-apoptotic activity is activated via its intera [...] (393 aa)									

Predicted Functional Partners:

SIRT1	NAD-dependent protein deacetylase sirtuin-1; NAD-dependent protein deacetylase that links transcriptional regulation direct...					●	●	●		0.999
RPA1	Replication protein A 70 kDa DNA-binding subunit, N-terminally processed; As part of the heterotrimeric replication protein ...						●	●	●	0.999
MDM2	E3 ubiquitin-protein ligase Mdm2; E3 ubiquitin-protein ligase that mediates ubiquitination of p53/TP53, leading to its degrad...						●	●	●	0.999
CREBBP	CREB-binding protein; Acetylates histones, giving a specific tag for transcriptional activation. Also acetylates non- histone p...					●	●	●		0.999
EP300	Histone acetyltransferase p300; Functions as histone acetyltransferase and regulates transcription via chromatin remodelin...						●	●	●	0.999
DAXX	Death domain-associated protein 6; Transcription corepressor known to repress transcriptional potential of several sumoyla...						●	●	●	0.999
ATM	Serine-protein kinase ATM; Serine/threonine protein kinase which activates checkpoint signaling upon double strand breaks...						●	●	●	0.999
HSP90AA1	Heat shock protein HSP 90-alpha; Molecular chaperone that promotes the maturation, structural maintenance and proper re...					●			●	0.999
SFN	14-3-3 protein sigma; Adapter protein implicated in the regulation of a large spectrum of both general and specialized signal...					●	●	●		0.999
TP53BP2	Apoptosis-stimulating of p53 protein 2; Regulator that plays a central role in regulation of apoptosis and cell growth via its i...					●	●	●		0.999

Figure9: In protein-protein interaction predicted Functional Partners Analysis

The TP53 output underscores p53's crucial role as both a tumour suppressor and a transcription factor that regulates cell cycle arrest and apoptosis. It highlights its dual function: halting cell division under stress and inducing programmed cell death via pathways like BAX and FAS activation or Bcl-2 repression. The predicted interaction partners, all with very high confidence scores (0.999), illustrate the complexity of p53's regulatory network. For instance, MDM2 is a known negative regulator that ubiquitinates p53 for degradation, while CREBBP and EP300 serve as co-activators that acetylate p53 to boost its transcriptional activity. SIRT1 counteracts this by deacetylating p53, influencing its stability and function. Partners such as ATM connect p53 to DNA-damage signalling, and RPA1 links it to replication-stress responses. Proteins like DAXX, SFN (14-3-3 sigma), and TP53BP2 further integrate p53 into apoptosis and checkpoint pathways, with HSP90AA1 aiding in its stabilization. Overall, this network emphasises p53's role as a hub protein, orchestrating stress responses, gene regulation, and apoptosis through a tightly controlled set of interactions.

PDBsum and ligplot

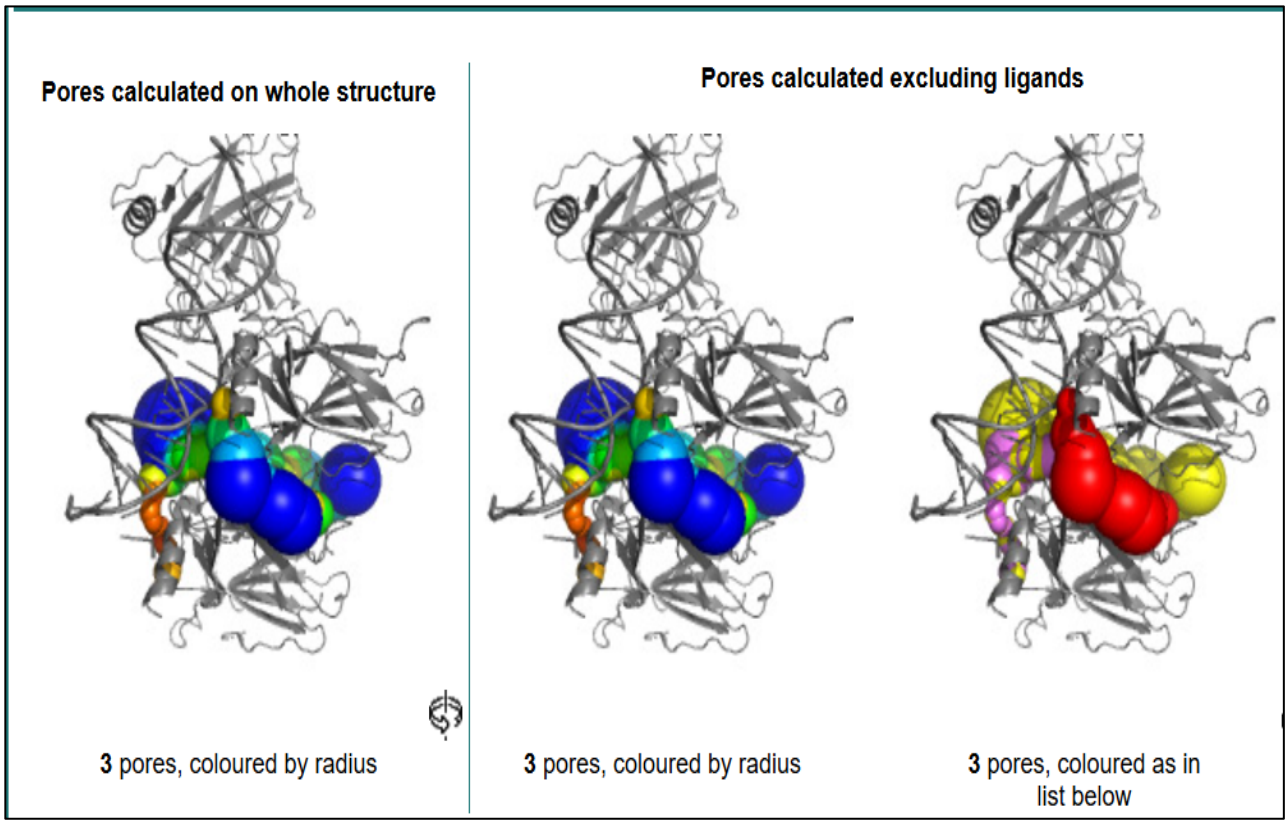

Figure 10: Pore Visualization analysis of sample 1TSR with PDBSUM

The final visualization compares pore calculations with and without ligands. Including ligands alters pore dimensions and accessibility, while excluding them reveals intrinsic structural pathways. The comparison demonstrates how ligand binding reshapes pore architecture, influencing polarity, hydrophobicity, and functional classification. This highlights the importance of considering ligand effects when analysing protein channels or cavities.

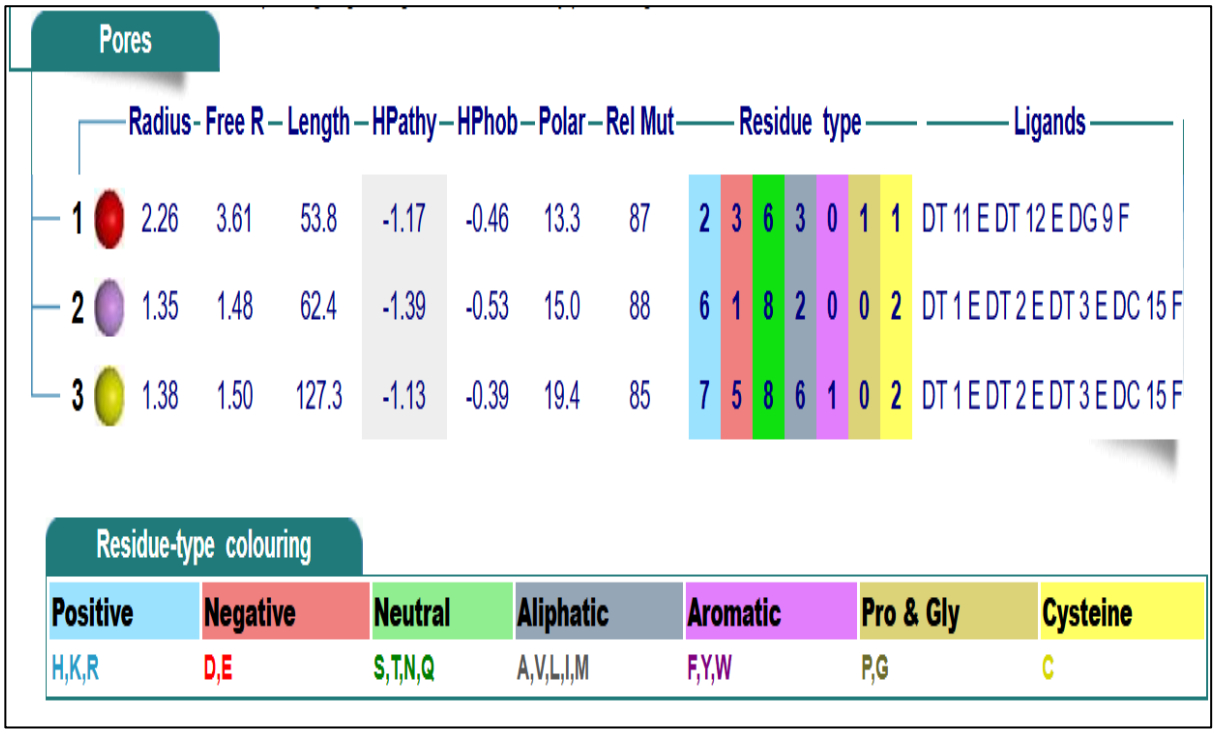

Figure 11: pore properties Analysis

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The pore analysis quantifies structural and chemical features of three pores, including radius, length, hydropathy, polarity, and residue composition. Each pore shows distinct profiles: for example, pore 1 has a larger radius and mixed residue types, while pore 3 is longer and more polar. The residue composition highlights contributions from charged, neutral, and hydrophobic residues, with associated ligands influencing accessibility. These metrics provide insight into how pores mediate transport, binding, or structural stability.

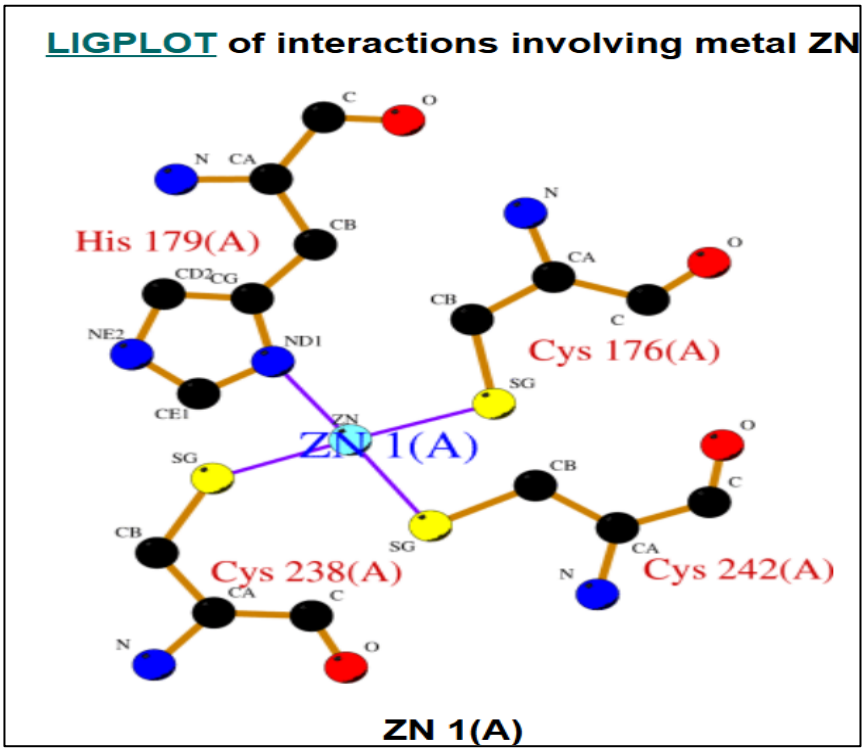

Figure 12: Ligplot analysis of metal ion Zinc in sample 1TSR

The LIGPLOT diagram shows a zinc ion coordinated by His179, Cys176, Cys238, and Cys242. The coordination bonds between zinc and sulphur/nitrogen atoms stabilize the protein's structure, forming a classic zinc-binding motif. Such sites are critical for maintaining fold integrity and often play roles in transcription factor activity, where zinc stabilizes DNA-binding domains.

B-Factor

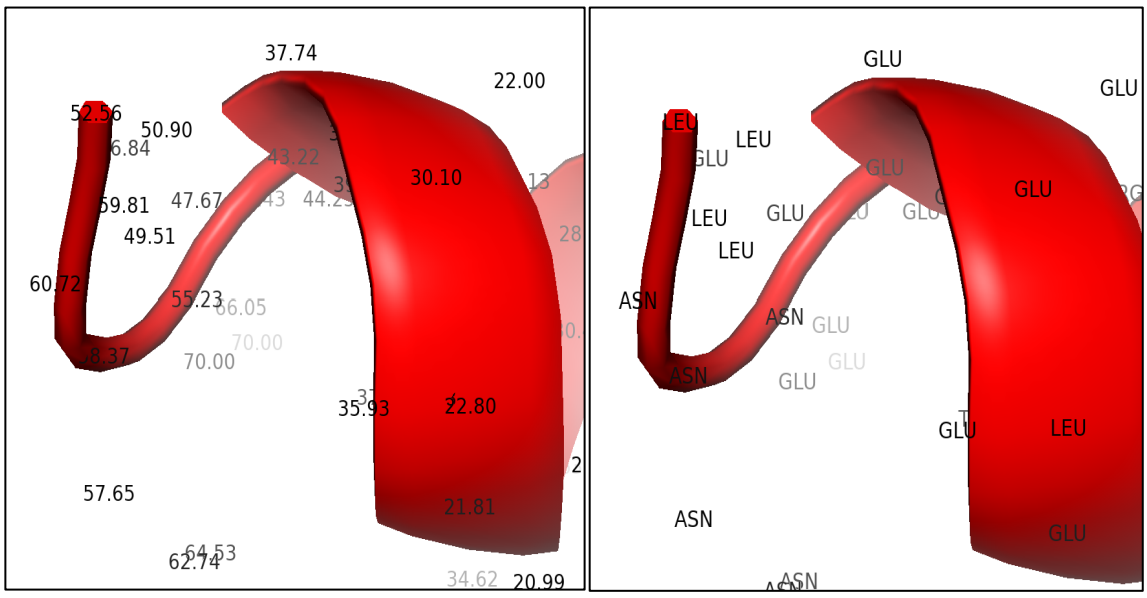

Figure 13: B-Factor analysis of sample antitumor protein at position 286 ASN aa 60.72

The B-factor analysis (represented by the ribbon with numerical values) and the 3D structural visualisation with labelled residues (ASN, LEU, GLU) together offer complementary insights into protein movement. The B-factor values indicate the extent of atomic displacement or flexibility within the protein backbone—higher values (around 70) show more mobile regions, whereas lower values (20–30) indicate more rigid, stable parts. When these are mapped onto the 3D ribbon, they reveal which amino acids are in flexible loops versus stable secondary structures, such as helices. Polar residues like GLU and ASN are often found in solvent-exposed areas with higher B-factors, whereas hydrophobic residues such as LEU usually reside in stable core regions with lower B-factors. Together, the two visualisations show how the placement of structures and the chemistry of residues relate to the protein's dynamic behaviour: the ribbon plot indicates flexibility, while the labelled 3D structure offers spatial context. This combined view helps pinpoint potential functional hotspots, flexible regions that could assist in binding or conformational changes, and rigid regions that maintain stability. Ultimately, the B-factor data enriches the structural model by illustrating the protein's dynamic landscape, linking static images with functional motions.

Discussion

This study explored the mutational profile of the TP53 gene in oral squamous cell carcinoma (OSCC) through next-generation sequencing (NGS) combined with structural bioinformatics analysis. TP53 is known as one of the most commonly mutated tumour suppressor genes in human cancers and is vital for maintaining genomic stability by controlling cell cycle arrest, apoptosis, and DNA repair processes. The results reveal that most TP53 mutations in OSCC occur within the DNA-binding domain (DBD), a critical region for the gene's transcriptional regulatory activity. NGS analysis showed that missense mutations are the most common type in TP53. These mutations cause amino acid changes that can affect the protein's structure or function. Several mutation hotspots identified in this study match well-known TP53 hotspot positions, such as R175, G245, R248, R273, and R282. These residues are highly conserved and are crucial for maintaining the protein's stability or binding with DNA. Changes at these sites are known to significantly weaken the tumour suppressor function of TP53, resulting in uncontrolled cell growth and tumour formation. Structural analysis using the crystal structure (PDB ID: 1TSR) provided valuable insights into how these mutations impact the three-dimensional shape of the TP53 protein. Many mutated residues were located within the DNA-binding interface or areas crucial for structural stability. For instance, mutations such as R248W and R273H occur at residues that directly contact DNA, disrupting sequence-specific DNA binding. Likewise, mutations like R175H and G245S affect residues vital for the stability of the DNA-binding domain, which can lead to protein misfolding or decreased stability. Analysis of domain and motif using InterProScan and PROSITE revealed that the mutations identified coincide with conserved functional regions of the TP53 protein. This indicates that changes within these regions could considerably impair the transcriptional activation of downstream genes that regulate the cell cycle and apoptosis. Disruption of TP53's transcriptional regulation is a key factor in the progression of tumors. Analysis of protein-protein interactions using the STRING database shows that TP53 acts as a key hub in a complex regulatory network involving proteins linked to DNA damage response, apoptosis, and cellular stress pathways. Notable partners include MDM2, ATM, ATR, and BAX, which collectively control TP53's stability and activity. Mutations that change TP53's structure could disrupt these interactions, potentially causing mis regulation of essential cellular pathways that normally prevent tumour development. Structural interaction analysis with PDBsum and LigPlot provided a visualization of residue-level contacts within the protein and between TP53 and DNA. [18] Several mutated residues engaged in hydrogen bonds and hydrophobic interactions crucial for protein stability and DNA binding. Mutations that disrupt these interactions can severely impair TP53's functional effectiveness. The B-factor analysis provided additional insight into TP53 protein dynamics. Areas with higher B-factor values indicate regions of increased structural flexibility.[19] Mutations in these flexible regions could further destabilise the protein and impair its function. Overall, combining NGS-based mutation profiling with structural bioinformatics offers a thorough understanding of how TP53 mutations influence OSCC development. This approach emphasizes the value of integrating genomic and structural information to uncover the molecular mechanisms behind cancer progression. Identifying mutation hotspots and key structural residues could aid in creating targeted therapies and personalized treatments for oral squamous cell carcinoma patients. [20,21]

Conclusion

1. Oral squamous cell carcinoma continues to pose a major global health issue due to its high prevalence, aggressive nature, and poor prognosis. Genetic changes are key in the initiation and progression of this cancer, with mutations in the TP53 gene being among the most important molecular events linked to OSCC development. This study focused on analyzing the mutational profile of TP53 through next-generation sequencing and assessing the

structural and functional impacts of these mutations using bioinformatics and structural biology techniques. The study showed that TP53 mutations mainly occur in the DNA-binding domain, which is vital for recognizing DNA sequences and controlling gene transcription related to cell cycle and apoptosis. The most common mutation type identified was missense mutations, aligning with earlier genomic research on oral cancer. These mutations can compromise the protein's structure, impair DNA binding, and eliminate its tumour-suppressing activity. Analysis of the PDB structure (1TSR) indicated that numerous mutation sites are located at conserved residues crucial for protein stability and DNA binding. Tools like MMDB, InterProScan, and PROSITE assisted in pinpointing key structural domains and conserved motifs within TP53. Mutations in these areas could greatly impact protein folding, stability, and function. Analysis of protein interactions with the STRING database revealed that TP53 functions as a key hub in cellular regulatory networks. It interacts with important regulators involved in the cell cycle, DNA repair, and apoptosis, such as MDM2, ATM, and BAX. Mutations that cause structural changes may disrupt these interactions, potentially leading to unchecked cell growth and tumor formation. Additionally, structural interaction analysis with PDBsum and LigPlot offered detailed insights into how TP53 interacts with DNA molecules. The identification of residues that participate in hydrogen bonds and hydrophobic interactions underscores their crucial role in preserving the protein's functional conformation. B-factor analysis identified areas of flexibility in the TP53 protein, indicating that mutations in these regions could further destabilize the structure and impair its function. These results underscore the crucial role of structural stability in preserving TP53's tumor suppressor activity. Overall, integrating NGS-based genomic profiling with structural bioinformatics offers a comprehensive view of the molecular mechanisms behind TP53 mutations in oral squamous cell carcinoma. This combined approach can help identify mutation hotspots, structural weaknesses, and potential therapeutic targets. Future research should prioritize integrating multi-omics datasets—such as transcriptomics, proteomics, and epigenomics to gain a more complete understanding of OSCC development. Moreover, experimentally validating the predicted structural impacts of TP53 mutations will advance targeted therapies and precision medicine approaches for oral cancer treatment..

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