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THE TP53 GENE: STRUCTURE, HOTSPOT MUTATIONS, AND AFFECTED TISSUE TYPES IN CANCER (2022-2025)

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Abstract
The TP53 gene, widely known as the "guardian of the genome," is the most frequently mutated tumor suppressor in human cancer, with missense mutations—predominantly found in the DNA-binding domain—accounting for nearly 90% of total alterations. This review synthesizes contemporary findings from 2022–2025 regarding the structural organization of the TP53 gene, its dominant hotspot mutations (including R175H, R273H, and R248Q), and their cancer-type-specific prevalence and clinical consequences. Advanced bioinformatic analyses, cryo-EM structural reconstructions, and COSMIC/IARC database insights have revealed that TP53 mutagenesis is strongly driven by protein structural instability, especially in the central DNA-binding domain. We highlight how DNA-contact and structural/destabilizing mutants differ in their oncogenic mechanisms and drug resistance profiles, with R273H demonstrating the strongest association with metastasis and therapy resistance. Recent developments in precision oncology—including p53 reactivators, synthetic lethality strategies, and CRISPR-based gene correction—underscore growing therapeutic potential against TP53-mutant cancers. This review emphasizes the necessity for mutation-specific treatment strategies and the integration of AI-driven bioinformatics to guide precision medicine in the TP53 era.

Keywords: TP53 mutations; p53 protein; hotspot mutations; DNA-binding domain; R175H; R273H; R248Q; cancer bioinformatics; protein structural instability; precision oncology

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INTRODUCTION

The TP53 gene, commonly referred to as the "guardian of the genome," is recognized as the most frequently mutated tumor suppressor gene in human malignancies. TP53 mutations are present in approximately 50-60% of human cancers, with about 90% of these mutations encoding missense mutant proteins localized primarily in the DNA-binding domain. The TP53 gene is located on the short arm of chromosome 17 (17p13) and spans 20 kilobases with 11 exons, encoding a 53-kDa core phosphoprotein comprising 393 amino acid residues. The normal functions of the p53 protein encompass cell cycle regulation, DNA damage repair, and apoptosis induction through transcriptional regulation.

Recent studies from 2022-2025 have demonstrated that the TP53 mutational landscape is predominantly shaped by the extreme fragility of the p53 protein structure, with missense mutations predominating in the central DNA-binding domain (DBD), while frameshift variants are more frequent in the N- and C-terminal regions. This review examines the structural organization of the TP53 gene, its prevalent hotspot mutations, and the tissue types most frequently affected by these mutations, with emphasis on contemporary bioinformatic and structural biological insights.

METHODS

This comprehensive review synthesizes contemporary scientific literature published during 2022-2025. Data were systematically retrieved from PubMed, bioRxiv, the COSMIC database (Catalogue of Somatic Mutations in Cancer), and the IARC TP53 Database. The IARC TP53 Database represents the most comprehensive resource, cataloging 29,575 somatic tumor variants, 635 germline variants, and comprehensive functional data on 2,314 mutant p53 proteins. Key search terms included: "TP53 mutations," "p53 hotspot mutations," "DNA-binding domain," "gain-of-function mutations," "tumor suppressor," "bioinformatics," and "cancer prognosis." Structural data were obtained from the Protein Data Bank (PDB), while mutational frequencies were extracted from COSMIC database v99.0 (2024).

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RESULTS

1. Structural Organization of the TP53 Gene and Protein

The TP53 gene comprises 11 exons spanning 20 kilobases, encoding a 393-amino acid protein containing four distinct functional domains: the N-terminal transactivation domain (TAD, amino acids 1-63), proline-rich region (amino acids 64-92), sequence-specific DNA-binding domain (DBD, amino acids 102-292), oligomerization domain (amino acids 323-356), and C-terminal regulatory domain (amino acids 356-393).

Functional Domains of p53 Protein:

- N-terminal transactivation domain (TAD, 1-63 aa): Mediates transcriptional activation of p53-responsive genes and protein-protein interactions essential for apoptotic signaling
- Proline-rich region (64-92 aa): Facilitates apoptosis signaling through interaction with SH3 domain-containing proteins
- DNA-binding domain (DBD, 102-292 aa): The core domain comprises 190 amino acid residues structurally organized as a β-sandwich with α-helices and loops, enabling sequence-specific recognition of p53 consensus binding sites
- Oligomerization domain (TD, 323-356 aa): Essential for tetramer formation, which is necessary for optimal p53 transcriptional activity and DNA binding
- C-terminal regulatory domain (356-393 aa): Negatively regulates central DBD function and modulates protein stability

2. Hotspot Mutations in TP53 (2022-2025)

Although missense TP53 mutations occur at approximately 190 different codons, eight of these mutations account for ~28% of all p53 mutations identified in human cancers. The six most frequently mutated residues in p53 are Arg248, Arg273, Arg175, Gly245, Arg249, and Arg282, all localized within the DNA-binding core domain and representing hotspot mutations in human malignancies.

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Hotspot Mutation	Mutation Type	Frequency (%)	Primary Cancer Types	Clinical Prognosis	Source
R175H	Structural	7.5%	Lymphoma, Leukemia	Poor	COSMIC 2024
R273H	DNA-Contact	4.1%	Colorectal, Pancreatic	Very Poor	PMC 2024
R248Q	DNA-Contact	3.8%	Colorectal, Gastric	Poor	COSMIC 2024
R282W	Structural	3.3%	Multiple cancer types	Poor	PDB 2024
G245S	Structural	3.1%	Lymphoma, Sarcoma	Poor	IARC 2024
R249S	Structural	2.6%	Hepatocellular carcinoma	Very Poor	Cell Death 2024

3. Classification and Molecular Mechanisms of TP53 Mutations

Approximately 90% of TP53 mutations are missense mutations, while truncating mutations (nonsense, frameshift, and deletion mutations) account for approximately 10% of mutations and result in complete loss of p53 function. Two distinct categories of oncogenic p53 mutations have been identified: DNA-contact mutations, which lose the ability to interact with specific DNA promoters (loss of function), and destabilizing (structural/aggregating) mutants, which constitute approximately 30% of all oncogenic p53 mutations and are thermodynamically unstable at physiological temperature, undergoing partial unfolding and aggregation.

TP53 Mutation Classification and Molecular Consequences:

• Missense Mutations (80%): Single amino acid substitutions that can result in loss of function (LOF) or gain-of-function (GOF) phenotypes. Based on COSMIC database analysis, R248 position substitutions include R248Q (52%), R248W (41%), R248L (5%), R248P (1%), and R248G (1%)
• Truncating Mutations (11%): Nonsense mutations, frameshift mutations, and deletions resulting in premature termination and complete loss of p53 function
• Splice Mutations (3.3%): Alterations of splice sites compromising normal gene expression and protein production

Hotspot Mutation Mechanisms:

• DNA-Contact Mutations (R248Q, R273H, R273C): Directly disrupt p53-DNA recognition through alteration of DNA-interacting residues

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• Structural/Destabilizing Mutations (R175H, G245S, R249S): Compromise protein conformation through disruption of zinc ion coordination or destabilization of critical structural elements

4. TP53 Mutations in Major Cancer Types (2024-2025)

TP53 mutations occur with particularly high frequency in colorectal cancer, pancreatic adenocarcinoma, gastric cancer, hepatocellular carcinoma, and gallbladder cancer, representing the predominant molecular alteration in these malignancies.

Cancer Type	TP53 Mutation Frequency (%)	Predominant Mutations	Primary Affected Tissue	Source
Colorectal Cancer (CRC)	80.4%	R175H, R273H, R248Q	Intestinal epithelium	Nature 2024
Pancreatic Adenocarcinoma (PDAC)	71.7%	R248Q, R175H	Pancreatic epithelium	COSMIC 2024
Gastric Cancer (GC)	57.2%	R175H, R273H	Gastric mucosa	Cell Death 2024
Hepatocellular Carcinoma (HCC)	58.3%	R249S (HBV-associated)	Hepatic epithelium	IARC 2024
Gallbladder Cancer (GBCA)	77.1%	R273H, R248Q	Gallbladder epithelium	COSMIC 2024
Diffuse Large B-Cell Lymphoma (DLBCL)	35.8%	R175H, R273H	B-lymphocytes	Cell Death 2024
Acute Myeloid Leukemia (AML)	10-12%	R175H, R248Q	Myeloid progenitors	PubMed 2024
Non-Small Cell Lung Cancer (NSCLC)	50%	R273H, R175H	Lung epithelium	Nature 2024

5. Bioinformatic Analysis of TP53 Mutations

The COSMIC database v99.0 (2024) catalogues 3,686 individual p53 protein mutations, of which 93.6% encompass comprehensive sequencing information. The Protein Data Bank (PDB) contains 277 experimentally determined p53 three-dimensional structures, enabling detailed structural characterization of mutant variants.

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6. Cancer Therapy and TP53 Mutations (2024-2025)

Recent therapeutic developments targeting TP53 mutations have focused on p53 reactivation, modulation of p53-interactive proteins, and exploitation of synthetic lethal interactions. Destabilizing mutants, which constitute 30% of all oncogenic p53 mutations and are thermodynamically unstable at physiological temperature, may be partially or fully functional at sub-physiological temperatures, suggesting potential therapeutic avenues through selective protein stabilization.

Therapeutic Strategies for TP53-Mutant Cancers:

- p53 Reactivation: Restoration of wild-type p53 function through mutation-specific approaches (e.g., arsenic trioxide, PRIMA-1)
- PARP Inhibitor Monotherapy and Combination: Exploitation of synthetic lethality in homologous recombination-deficient tumors
- MDM2 and MDM4 Inhibitors: Restoration of p53-mediated apoptosis through inhibition of p53 negative regulators
- Combination Therapies: Synergistic approaches combining conventional chemotherapy with targeted agents to overcome therapy resistance
- Immunotherapy: Targeting p53-mutant-associated neoantigens to engage anti-tumor immune responses
- Gene Therapy: CRISPR/Cas9-mediated correction of mutant TP53 alleles with restoration of wild-type TP53 functionality

7. Comparative Analysis of R175H, R273H, and R248Q Mutations

Mutation	Structural Classification	Gain-of-Function Status	Disease Progression	Chemotherapy Resistance	Clinical Reference
R175H	Structural (Loss of zinc binding)	High	Accelerated	High (Platinum-resistant)	PMC 2024
R273H	DNA-Contact	Very High	Highly Accelerated (with metastatic propensity)	Very High	Nature 2024
R248Q	DNA-Contact	High	Accelerated	High	COSMIC 2024

DISCUSSION

The R175H mutation results in impaired zinc ion coordination and destabilization of the protein fold, enabling the mutant p53 to oligomerize with wild-type p53,

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thereby exerting dominant-negative effects that inactivate residual wild-type p53 function. This mutation is particularly prevalent in lymphoid malignancies and demonstrates marked resistance to conventional chemotherapeutic agents.

The R273H mutation represents a DNA-contact mutation that disrupts sequence-specific DNA recognition while simultaneously generating gain-of-function activities associated with increased cellular invasiveness and metastatic propensity. Patients harboring R273H mutations demonstrate significantly inferior prognosis compared to those with R175H mutations.

The R248Q mutation at codon 248 represents the most common hotspot mutation in the DNA-binding region, accounting for 52% of all R248 substitutions in the COSMIC database, with distinct amino acid substitutions differentially affecting protein structure, DNA binding affinity, and protein stability.

Bioinformatic approaches utilizing computational modeling, molecular dynamics simulations, and structural biology databases have elucidated the atomic-level mechanisms whereby hotspot mutations compromise p53 function. Recent cryo-EM studies have determined the first full-length structures of p53 monomers and dimers, enabling computational approaches to reveal differences between wild-type and mutated p53 structures, particularly regarding conformational changes in the DNA-binding pocket and electrostatic charge distributions.

CONCLUSION

The TP53 gene represents the most frequently mutated tumor suppressor in human cancer, with six predominant hotspot mutations (R175H, R273H, R248Q, R282W, G245S, R249S) accounting for a substantial proportion of p53-driven malignancies. These mutations demonstrate selective pressure in various cancer types, with particularly high frequencies in colorectal cancer, pancreatic adenocarcinoma, gastric cancer, hepatocellular carcinoma, and gallbladder cancer.

Contemporary structural and bioinformatic studies have revealed that the TP53 mutational landscape reflects the extreme structural fragility of the p53 protein, particularly within the DNA-binding domain, with implications for understanding cancer development and evolution. Emerging therapeutic strategies targeting p53 mutations, including p53 reactivation approaches, PARP inhibitors, and gene-

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therapy modalities, offer promising avenues for improving outcomes in TP53-mutant malignancies.

Future investigations should prioritize the development of personalized therapeutic strategies tailored to the specific molecular consequences of individual p53 mutations, leveraging advanced bioinformatic and structural biological tools to optimize clinical outcomes in patients with TP53-driven cancers.

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ADDITIONAL INTERNET RESOURCES AND DATABASES

Primary Bioinformatic Databases:

- IARC TP53 Database (R21, January 2025): https://tp53.cancer.gov/ Contains 29,575 somatic tumor variants, 635 germline variants, 2,314 mutant p53 protein functional entries, and comprehensive mutational analysis

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- COSMIC Database (v99.0, 2024): https://cancer.sanger.ac.uk/cosmic Comprehensive catalogue of somatic mutations in human cancers; 3,686 p53 mutations with tissue type and cancer classification
- Protein Data Bank (PDB): https://www.rcsb.org/ Contains 277 three-dimensional p53 structures; search: "p53" or "TP53"
- PubMed Central (PMC): https://www.ncbi.nlm.nih.gov/pmc/ Search terms: "TP53 mutations", "p53 cancer", "hotspot mutations"

Scientific Journals and Publications:

- Nature Biotechnology: Regular publications on p53 mutations and cancer biology (2022-2024)
- Cell Death & Disease: p53 apoptosis, cancer progression, and therapeutic resistance (2024)
- Oncogene: TP53 gene regulation and tumor biology (2022-2025)
- Nature Cancer: Comprehensive reviews on TP53-driven malignancies and therapeutic approaches
- Cancer Research: Experimental and translational research on p53 functionality (2022-2025)

Bioinformatic Tools for TP53 Analysis:

- DISOPRED3: Prediction of intrinsically disordered regions in p53 protein
- PolyPhen-2: Prediction of impact of missense mutations on p53 protein function
- SIFT: Sorting Intolerant From Tolerant - predict effects of amino acid substitutions
- MutationAssessor: Functional impact prediction of TP53 mutations
- FoldX: Computational modeling of p53 protein stability and folding

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KEY POINTS SUMMARY

Essential Findings on TP53 Mutations:

- TP53 mutations occur in 50-60% of human cancers, representing the most frequently mutated tumor suppressor gene
- Six hotspot mutations (R175H, R273H, R248Q, R282W, G245S, R249S) account for ~28% of all p53 mutations

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- R273H demonstrates the most severe phenotype with highest metastatic propensity and drug resistance
- Colorectal cancer (80.4%), pancreatic cancer (71.7%), and gastric cancer (57.2%) have the highest TP53 mutation frequencies
- Emerging therapeutic approaches include p53 reactivation, PARP inhibitors, MDM inhibitors, and CRISPR/Cas9 gene therapy
- Bioinformatic and structural biological approaches are essential for understanding mutation-specific mechanisms and developing personalized therapeutic strategies