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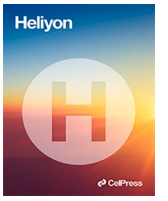

Review article

# The importance of protein domain mutations in cancer therapy

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ABSTRACT

Cancer is a complex disease that is caused by multiple genetic factors. Researchers have been studying protein domain mutations to understand how they affect the progression and treatment of cancer. These mutations can significantly impact the development and spread of cancer by changing the protein structure, function, and signalling pathways. As a result, there is a growing interest in how these mutations can be used as prognostic indicators for cancer prognosis. Recent studies have shown that protein domain mutations can provide valuable information about the severity of the disease and the patient's response to treatment. They may also be used to predict the response and resistance to targeted therapy in cancer treatment. The clinical implications of protein domain mutations in cancer are significant, and they are regarded as essential biomarkers in oncology. However, additional techniques and approaches are required to characterize changes in protein domains and predict their functional effects. Machine learning and other computational tools offer promising solutions to this challenge, enabling the prediction of the impact of mutations on protein structure and function. Such predictions can aid in the clinical interpretation of genetic information. Furthermore, the development of genome editing tools like CRISPR/Cas9 has made it possible to validate the functional significance of mutants more efficiently and accurately. In conclusion, protein domain mutations hold great promise as prognostic and predictive biomarkers in cancer. Overall, considerable research is still needed to better define genetic and molecular heterogeneity and to resolve the challenges that remain, so that their full potential can be realized.

## 1. Introduction

Cancer is a complex disease characterized by uncontrolled growth and division of cells in the body. The disease is caused by genetic and environmental factors which lead to the accumulation of mutations [1]. It is considered a leading cause of death in many countries. In the United States alone, it is predicted that there will be 1,958,310 new cancer cases and 609,820 cancer-related deaths in 2023 [2]. In India, cancer cases are estimated to increase by 12.8 percent in 2025 as compared to 2020 [3]. Cancer treatment typically involves a combination of surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy, or a combination thereof [4]. However, these conventional treatments are often ineffective due to the development of multidrug resistance and severe side effects [5]. Furthermore, drugs currently available for cancer treatment have drawbacks such as poor selectivity, limited pharmacodynamic properties, and poor oral bioavailability [6]. Therefore, there is a critical need for novel treatment strategies to address the limitations of current cancer therapies. Developing effective diagnostic and treatment methods for cancer is an area of great interest and challenge

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[7]. Numerous studies have been conducted to identify mutations in genes that play a role in the development of cancer [8]. The primary role of mutations in oncogenes has been widely recognized, which has led to an extensive screening of clinical samples and identification of thousands of cancer-associated gene mutations using next-generation sequencing [9,10]. These mutated genes serve as biomarkers that help in determining the tumor characteristics and subsequently guide the selection of appropriate cancer treatment [11,12]. Although scientists have made significant progress in identifying genes that are closely linked to cancer, they lag behind the genomic (transcriptomic) analysis [13]. Comprehensive global proteomics analysis has revealed only a small percentage of single nucleotide variants detected by DNA and RNA sequencing as single amino acid variants [14,15]. It's crucial to conduct proteomic analysis of mutations, as it can help develop cancer biomarkers and identify new pharmacological targets for effective cancer therapy [16]. It is possible that changing the order of amino acids in a protein may not lead to a loss of protein function, but can alter its structure [17]. Recently, computational predictive models have been developed to assist experimental studies in drug discovery, specifically virtual screening based on drug target protein interaction (DTI) [18]. There are two types of virtual screenings ligand based and structure based [19]. These methods come with limitations such as difficulty in discovering new scaffolds and obtaining the 3D structures of the proteins [20]. To address these precincts in drug discovery new computational approaches have developed incorporating machine learning and networking analysis [21].Mutations in protein domains can hinder the normal functioning of proteins [22,23]. Therefore targeting the functional domains can be an effective therapeutic approach for cancer [24]. Many computational predictive models have been developed based on chemogenomic-based drug/compound-target protein domain interaction predictive systems using publicly available databases such as ChEMBL, PubChem, UniProtKB, and InterPro. One of such tool developed in recent times is "DRUIDom" [25]. This approach is based on drug associating with protein domains based on their structural properties. This makes likely that other proteins containing the same mapped domain(s) will have the necessary structural properties to interact with the drug of interest [26].

Protein domains can be affected by mutations, which may disrupt their regular functions [27]. The gene-based approach used in computational structural studies does not consider the position of the mutation within the gene or the mutation's functional context. However, by examining the impact of mutations on specific sections of a protein, we can gain valuable insights, as illustrated in Fig. 1 [28–30]. Targeting protein domain mutations is a superior method because it is more precise [31]. This approach involves mapping mutation positions to specific domains that are driving tumorigenesis. By doing so, targeted therapies can be selected based on the genetic alterations [26]. Targeting domain mutations can also offer valuable information about disease severity and modulate specific signalling pathways, leading to better outcomes with reduced toxicity [32]. Studying the effect of protein domain mutations on cancer prognosis has become increasingly important in recent years [33]. These mutations can provide valuable insights into the severity of the disease and its response to treatment. Mutations in specific domains such as P53, PI3K, tyrosine kinase, zinc finger, and catalytic protein domains have been found to be significant in cancer [34–36]. For instance, P53 mutations, which are common in many cancers, can cause uncontrolled cell proliferation by undermining its tumor-suppressor activity. These mutations can lead to severe illness and therapeutic resistance [37]. PI3K mutation activates signalling pathways that promote cell survival and proliferation. They are common in breast, ovarian, and other malignancies, requiring specific treatments [38]. Mutations in the tyrosine kinase domain activate growth-promoting signals constitutively [39]. In leukemia and lung cancer, targeted tyrosine kinase inhibitors have transformed treatment [40]. Zinc finger domain mutations disrupt gene regulation, promoting cancer [41]. These mutations underscore the intricate nature of cancer genetics and underscore the critical need for personalized treatments in the ongoing pursuit of better cancer therapies and outcomes [42]. Understanding their effects can inspire new treatments. These mutations highlight the complexity of cancer genetics and the need for personalized treatments, reflecting the ongoing search for better cancer treatments and patient outcomes [43]. It is important to examine the role of protein domain mutation across various cancer types to develop targeted therapies [44], estimate the prognostic value of the disease, personalize therapies to specific mutations, identify the mutations that may confer resistance to cancer treatment, detect cancer development early, provide critical information in cancer biology and in clinical trials [45]. Recent studies have shown that protein domain mutations can serve as prognostic indicators in various types of cancer [46]. For example, mutations in Telomerase reverse transcriptase (TERT) genes, positioned −124 and −146 bp upstream from the ATG start site, increase TERT promoter activity by creating GGAA consensus binding sites for ETS transcription factors and increase the aggressiveness of glioblastoma (GBM) [47,48]. These mutations are independently associated with poor survival and disease

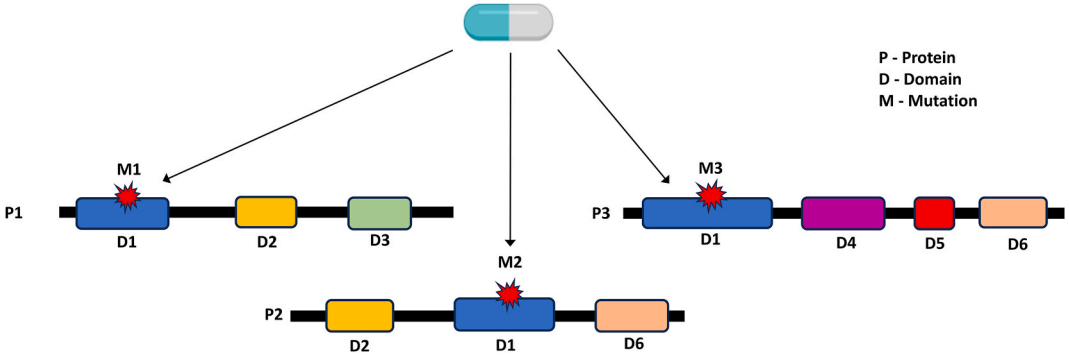


**Fig. 1.** Schematic representation of drug targeted similar domain of different mutated proteins.

relapse of GBM [49,50]. Another study evaluating 126 patients with non-small cell lung cancer (NSCLC) showed that targeting the mutant KRAS G12C (G domain) by AMG510 (Sotorasib) allowed for direct pharmacological inhibition of KRASp.G12 mutations and increased the overall response rate significantly [51,52]. Furthermore, novel most-potent-in-class natural inhibitors, selective inhibitors approved for clinical development, could extend patient life and improve the quality of life [53,54].

Current research in cancer is focused on studying the mutations in the cancer genomes to identify specific mutations in protein domains that may be associated with a poor prognosis [55]. Bioinformatics studies of mutations in protein domains in ovarian cancer also reveal therapeutic targets and prognostic indicators [56]. However, protein domain mutations as prognostic indicators in cancer still face challenges due to the complexity of the molecular pathways of cancer growth and the potential for mutational interactions. Despite these challenges, mutation patterns can still predict disease prognosis [57]. For instance, tumors with many alterations in DNA repair genes such as BRCA1 and BRCA2 in the ovarian cancer genome can act as biomarkers in predicting the disease [58]. It is worth noting that detecting rare or unusual mutations may require large samples and time-consuming genetic analysis. This review aims to provide an overview of protein domains and their functions and investigate the impact of mutations in protein domains on the onset and progression of cancer. It seeks to explore the underlying mechanisms of how these mutations affect cancer and identify the protein domains that are most frequently mutated in cancer. The study will also discuss the clinical relevance of protein domain mutations as prognostic and predictive biomarkers in cancer. The rationale of the study is to increase our understanding of the role of protein domain mutations in cancer and identify potential therapeutic targets and prognostic and predictive biomarkers for cancer patients. By examining the mechanisms underlying the impact of protein domain mutations on cancer and identifying the most frequently mutated protein domains in cancer, we can gain insights into the molecular pathways involved in cancer development and progression. This knowledge can be used to develop targeted therapies that address the underlying genetic mutations in cancer cells, leading to more effective treatments and improved patient outcomes. Additionally, we can identify new ways to personalize cancer treatment and enhance patient care by exploring the clinical relevance of protein domain mutations as prognostic and predictive biomarkers. Further, this review will explore the relationship between mutations in protein domains and cancer development. It covers the various effects of different types of mutations, the mechanisms that underlie their impact, and how protein domain mutations can act as biomarkers for predicting cancer prognosis and response to targeted therapies. Moreover, it highlights the most frequently mutated protein domains in cancer and their potential as therapeutic targets. It discusses the challenges and future directions in using protein domain mutations as biomarkers.

## 2. Protein domain mutations and cancer

Mutations refer to alterations in the DNA sequence, which may involve single nucleotide changes or structural rearrangements [59]. Mutations play a significant role in the development and progression of cancer [60]. These genetic changes can affect oncogenes and tumor suppressors, causing uncontrolled cell growth by disrupting essential regulatory pathways [61]. Mutation analysis is crucial in identifying these genetic aberrations that contribute to malignancy [62]. Tumor heterogeneity occurs when mutations lead to the formation of distinct subclones within tumors. This presents a challenge for targeted therapies. Additionally, mutations contribute to therapeutic resistance, so ongoing research is necessary to overcome this challenge [63]. Precision medicine uses knowledge of specific mutations to offer targeted therapies for improved cancer management. This opens up the possibility of personalized treatment strategies in the evolving field of oncology [64].

### *2.1. Overview of protein domains and their functions*

Domains, which are internal protein structures, play a crucial part in the assembly process. These protein domains are conserved across all species [49–52]. Many novel protein domains identified using computational methods and high-throughput sequencing improve the understanding of the structure and function of proteins [52]. For example, the biological roles of certain protein domains, such as zinc finger domains, have been studied. It has been established that it is involved in ubiquitination and can also function as a DNA-binding domain, demonstrating that domains play a crucial [53,65]. Recent studies discovered that a protein domain controls transcription, disclosing gene expression, DNA repair, and RNA processing [54,66–68]. In addition, new research has found protein domains that control protein synthesis. These domains have shed light on the intricate regulatory systems that control protein synthesis and may lead to the development of innovative cancer therapies [69,70]. Therefore, understanding the evolution of proteins in organisms requires a complete understanding of protein domains.

### *2.2. Protein domain mutations and their effects on cancer onset and progression*

Protein structure and function changes brought on by protein domain mutations may contribute to the onset and progression of cancer. Much research has investigated how different protein domain changes impact the development and spread of cancer [71–74]. This section discussed the most typical varieties of protein domain mutations.

#### *2.2.1. Missense mutations*

Missense mutations were the most prevalent form of mutation in protein domains after assessing the genomic data from over 8657 tumors representing 32 distinct cancer types [75–77]. Another study found that missense mutations make up about 88% of the gene variants in the COSMIC Catalog of Somatic Mutations in Cancer [78]. Missense mutations happen when a single nucleotide alteration modifies the protein's amino acid sequence. The research also raises the possibility that various cancer types may have unique

carcinogenesis pathways. For instance, the study discovered that lung and colorectal cancer typically had mutations in the KRAS gene, which codes for a protein essential for cell signaling, and that many of these changes were identified in the protein's GTPase domain [79].

### 2.2.2. Nonsense mutations

A nonsense mutation causes the coding sequence of an mRNA to contain an early termination codon. This mutation stops translation and, in most cases, results in the synthesis of a truncated and dysfunctional protein, which in turn causes cancer [80]. According to COSMIC mutational data, nonsense mutations account for 40% of the variance [78]. The nonsense mutations in the tumor suppressor gene play a crucial role in cancer development. For instance, cancer prognosis is affected by nonsense mutations in tumor suppressor genes like TP53, RBI, and PTEN. Recent mutational landscape analyses found that nonsense mutations were detected in 11% of TP53, 25–34% of RBI, and 17.3% of PTEN [81]. Also, the COSMIC database (http://cancer.sanger.ac.uk/cosmic/) revealed that the percentage of nonsense mutations in TP53, BRCA1, PTEN, and APC samples was 7.7% of 2129 TP53 mutations, 11.4% of 413 BRCA1, 15.8% of 3250 PTEN, and 41.5% of 4216, respectively. However, nonsense mutations are less common. Most of them are found close to stopping codons in genes connected to cancer, making them less harmful compared to the nonsynonymous and synonymous ratio [80].

### 2.2.3. Frameshift mutations

Translational frameshift is caused by the insertion or deletion of a nucleotide in the triple codon nature of gene expression, which disrupts the gene's function. Microsatellite instability (MSI) causes a large number of these insertion and deletion (INDELS) events in repetitive DNA sequences [82]. According to a cosmic mutational data study, 23% of mutations are recorded as frameshifts [78]. Recent studies show frameshift mutations are the most prevalent form of mutations linked to colorectal cancer [83]. MSI-induced frameshift mutations account for 15% of colon cancer cases [84]. For instance, frameshift mutations (interstitial deletions) in the N-terminal region of APC's -catenin binding domain leads to APC's functional gain and plays a role in the stimulation of the Wnt signalling pathway, which is crucial for the growth of colorectal cancer. TP53 frameshift mutations are seen in more human malignancies [85].

### 2.2.4. Split site mutations

Splicing needs to be controlled to determine a cell's identity and developmental programs, and its dysregulation is directly connected to conditions like cancer [85]. Even it disrupts the protein-protein interaction pathways that lead to tumor formation [86,87]. Several investigations have discovered a connection between malignancies and alternative splicing [88,89]. Spliceosome mutations in cancer have brought attention to the importance of the spliceosome pathway as a direct contributor to carcinogenesis and prompted questions regarding the molecular mechanisms and functional implications of these aberrations [90]. Recent decades have seen recurrent somatic alterations in human solid tumors in various parts of the splicing system. Since the HEAT (Huntingtin, elongation

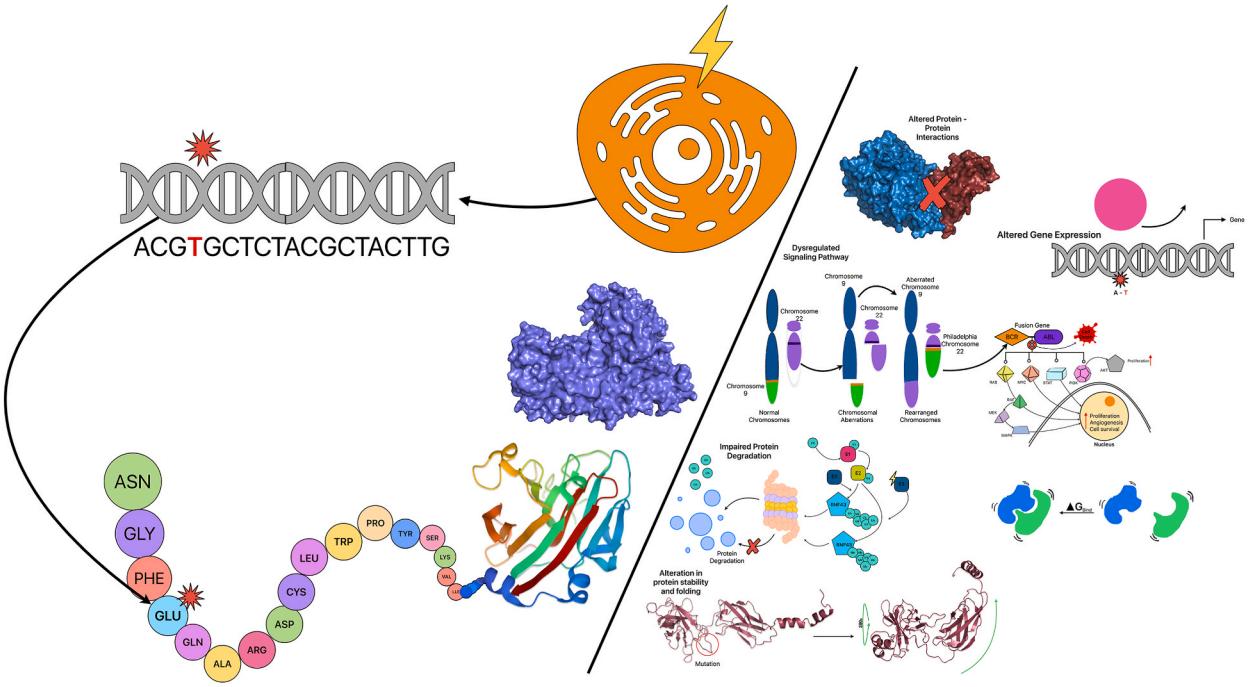


**Fig. 2.** Representation of mechanisms underlying the impact of protein domain mutations in cancer.

factor 3) domain of SF3B1 is the most significant component of the SF3B complex and a crucial element in spliceosomes [91], abnormalities in this domain can result in improper splicing and cancer [92].

## 3. Mechanisms underlying the impact of protein domain mutations on cancer

### 3.1. Altered protein-protein interactions

Protein domains frequently mediate protein-protein interactions; mutations in these domains can change a protein's capacity to interact with other proteins [93]. For instance, a mutation in the DNA-binding region of the p53 gene at position R175H can block the interaction of RSL1D1 and p53 and activate downstream tumor-suppressing pathways, resulting in colorectal cancer [94,95]. Similarly, mutations in the exons 18–21 of EGFR allow the kinase domain to interact abnormally with downstream signalling molecules through the PI3K/AKT and MAPK/RAF pathways, resulting in uncontrolled cell proliferation [96,97]. Recent studies have revealed further information about the effects of mutations in protein-protein interaction domains in cancer. For instance, multi-omics screening research shows that EGFR is a crucial modulator of cancer progression and that mutations in the LGR4 domain cause downstream signalling to do so [98]. Furthermore, it was shown that in breast cancer, mutations in the TAZ domain of the transcriptional coactivator YAP enhanced its capacity to interact with TEAD transcription factors and activate downstream oncogenic pathways [99] (Fig. 2).

### 3.2. Dysregulated signalling pathways

Many protein domains are involved in the signalling networks that control cellular activities such as proliferation, differentiation, and death. Mutations in these domains can result in constitutive activation of these pathways, promoting unchecked cell proliferation and the emergence of cancer. For instance, in chronic myeloid leukemia, mutations in the BCR-ABL fusion protein's kinase domain result in the constitutive activation of the downstream signalling cascade, which promotes unchecked cell growth and the growth of cancer (Fig. 1). Recent studies have further supported the contribution of dysregulated signalling pathways to the emergence of cancer. For instance, mutations in the RET's tyrosine kinase domain, which is fused in-frame to the NH2-terminal partner and the RET's TKD and COOH tail, encourage the activation of downstream oncogenic signalling pathways and lead to differentiated thyroid cancer (DTC) [100]. Similar to this, it has been shown that the G1202R mutation in the kinase domain of the ALK receptor causes non-small cell lung cancer by promoting resistance to ALK inhibitors (alectinib, crizotinib) via activating downstream signalling pathways [101].

### 3.3. Impaired protein degradation

Defective protein degradation is caused by the accumulation of mutations in oncoprotein domains, including TP53, AKT1, and IDH1, which are highlighted as candidate genes for post-translational modification (PTM) related processes. These PTM mutations disrupt the control of protein deterioration, causing a buildup of oncogenic proteins that aid in the development of cancer [102]. For example, hypoxia-inducible factor 1 (HIF1) can accumulate as a result of mutations in the von Hippel-Lindau tumor suppressor protein, which has a ubiquitin ligase domain and can prevent it from targeting HIF1 for destruction, activating downstream tumour-promoting pathways [103]. Recent studies have provided further information on how defective protein breakdown contributes to cancer development. Similarly, mutations in the E3 ubiquitin ligase of RNF43 were found to impair its degradation and promote the activation of Wnt signalling pathways in colorectal cancer [104,105].

### 3.4. Alterations in protein stability and folding

Protein misfolding and aggregation are caused by protein stability and folding changes. As several protein domains are involved in these processes, changes to these domains can affect protein stability and folding. These aggregation factors can affect cellular functions and promote the growth of cancer. When the p53 tumor suppressor protein, which has a DNA-binding domain and a tetramerization domain, is altered, this can disrupt the protein's stability and folding, accumulating misfolded p53 and activating oncogenic pathways [106]. In addition, the C-terminal domain of BRCA1 (BRCT) p.M1775R variation modifies the interaction between BRCT and histone deacetylase in breast cancer. In this variation, R1835 rotates away from Q1811 to form a new salt bridge with E1836, and R1699 maintains the salt bridge with D1840 but no longer contacts it and instead coordinates an anion [107,108]. Recent studies have provided additional information on how protein stability and folding alterations contribute to cancer development. In esophageal squamous cell carcinoma (ESCC), mutations in the RRM domain of the RNA-binding protein TIA1 were discovered to alter its RNA-binding activity and promote the creation of stress granules, which are associated with the development of cancer [108,109]. In addition, it has been revealed that mutations in the TET2 protein, which contains a catalytic domain that regulates DNA methylation, impair protein folding and lead to an accumulation of incorrectly folded TET2, which promotes the development of myeloid malignancies [110].

### 3.5. Altered gene expression

Protein domain mutations can alter gene expression patterns, leading to abnormal protein function and cancer. Mutations in the BET family of proteins' bromodomain can cause dysregulation of gene expression in cancer cells, promoting the development and

spread of triple-negative breast cancer (TNBC) [111]. Moreover, an oncogene known as a master regulator of cell cycle entry and proliferative metabolism (MYC) promotes cell growth and proliferation. Mutations in the MYC basic helix-loop-helix leucine zipper (bHLH-LZ) domain, which is involved in dimerization and DNA binding of the MYC gene, and in the MYC transactivation domain (TAD), which is responsible for target gene activation, can result in overexpression or stabilization of the MYC gene, which eventually causes uncontrolled cell growth and division, leading to cancer [112].

### 3.6. Most frequently mutated protein domains in cancer

Various biological processes trigger cancer development and spread, including mutations in crucial proteins and signalling networks. A key component of cancer genetics is the identification of commonly changed protein domains in cancer [39]. As mentioned, domains are essential for controlling cell proliferation, differentiation, and survival. These domains are susceptible to mutations that might cause uncontrolled cell proliferation, which can be a hallmark of cancer [113]. In our earlier research, we discovered several protein domains that are frequently mutated in a range of malignancies like p53, PI3-Kinase alpha (PI3Ka), Nebuline (NEBL), and zf-H2C2_2 [114]. Identifying these commonly altered protein domains has provided a crucial understanding of the molecular processes underpinning the development and spread of cancer. It has also revealed potential medicinal targets for the fight against cancer. The discovery of frequently mutated protein domains in cancer is just the start. It is essential for the creation of efficient cancer treatments to comprehend the functional implications of these mutations on protein-protein interactions and signalling cascades. It is also crucial to stress that not all mutations in these protein domains have functional consequences or influence the onset of cancer. Most of these mutations either happen in benign tumors or have no impact on cellular activity. The mutations that contribute to the emergence and spread of cancer must therefore be identified through further investigation.

### 3.7. Protein domain as therapeutic targets

Many proteins comprise numerous distinct domains and can serve as targets for therapeutic intervention [115]. Since protein domains are crucial to controlling the wide range of biological processes and are referred to as structural and functional units of a protein, mutations in these domains may lead to cancer. Many independent studies reveal that clustering these mutations at specific catalytic positions leads to cancer [116]. Hence, targeting these regions can be promising for creating novel therapeutics. Further, due to the conservatory nature of the domains amongst proteins, these can act as potential targets with a variety of therapeutic uses with minimal likelihood of unintended side effects creating room for personalized medications. For example, the most common mutations in the tyrosine kinase domain (TKD) of the FMS-like tyrosine kinase (FLT3) gene were targeted by Midostaurin [117–119], Gilteritinib [120,121], Quizartinib [122,123] Numerous examples of powerful drugs target specific protein regions (Table 1). These cancer

**Table 1**
List of Protein domains with targeted drugs (* [58]). protein domains have been predicted as frequently mutated domains and reported in the DCMP database.

| Protein Domain | Protein Domain Name | Function | Potential Therapeutic Target | Drug Names | Reference |
|---|---|---|---|---|---|
| KRAS | Kirsten rat sarcoma viral oncogene homolog domain | Regulate cell growth and differentiation | KRAS inhibitors | Sotorasib, Adagrasib | [162,163] |
| TP53* | Tumor protein p53 domain | Tumor suppressor, DNA repair and apoptosis | TP53 activators | Prima-1, APR-246 | [164,165] |
| PIK3CA* | Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha domain | Regulate cell growth, differentiation and survival | PI3K inhibitors | Alpelisib, Idelalisib, Copanlisib | [166–168] |
| PTEN* | Phosphatase and tensin homolog domain | Tumor suppressor, negative regulator of PI3K-AKT signaling pathway | PTEN activators | VO-OHpic, SF1670 | [169,170] |
| BRCA1/2* | Breast cancer 1/2 domain | Tumor suppressor, DNA repair | PARP inhibitors | Olaparib, Rucaparib, Talazoparib | [171–173] |
| CDK4/6 | Cyclin-dependent kinase domain | Regulate cell cycle progression and transcription | CDK inhibitors | Palbociclib, Ribociclib, Abemaciclib | [174–176] |
| BCR-ABL* | Breakpoint cluster region-Abelson tyrosine kinase domain | Oncogenic fusion protein, constitutively active tyrosine kinase | BCR-ABL inhibitors | Imatinib, Dasatinib, Nilotinib | [177–179] |
| EGFR | Epidermal growth factor receptor domain | Regulate cell proliferation and survival | EGFR inhibitors | Gefitinib, Erlotinib, Afatinib | [180–182] |
| HER2 | Human epidermal growth factor receptor 2 domain | Regulate cell growth and differentiation | HER2 inhibitors | Trastuzumab, Pertuzumab, Ado-Trastuzumab Emtansine | [183–185] |
| BCL-2* | B-cell lymphoma 2 domain | Anti-apoptotic protein, involved in cancer cell survival | BCL-2 inhibitors | Venetoclax, Navitoclax | [186,187] |
| NTRK1/2/3 | Neurotrophic tyrosine receptor kinase domain | Regulate neuronal development and differentiation | NTRK inhibitors | Larotrectinib, Entrectinib | [188,189] |
| RET | Rearranged during transfection domain | Regulate cell growth and differentiation | RET inhibitors | Selpercatinib, Cabozantinib | [190,191] |

medications have transformed how cancer is treated and set the bar for developing domain-specific therapeutics.

Protein domains are proteins' functional units that function through their constituent domains. The protein sequence is subject to mutations in natural evolution and somatic development, especially in cancer tissues. Accumulation of mutation in oncogenes and tumor suppressor genes causes cancer. Very little research has been conducted at the domain level in the last ten years. Among those, the domain-mutation landscape across 21 cancer types accomplished identifying the domains with high mutational density in specific tissues (Table 2). In addition, the domain-level study helps identify known and novel candidate driver mutations. It has shown that these domain instances play important roles in cell-cell communication and, thus, are essential for the cell's normal functioning. At the same time, the NGS analysis is still far away from analyzing the mutations at the protein domain level, and this would provide a broad spectrum of opportunities for the researchers to uncover the novel and candidate mutations not only in cancer but also in other diseases.

## 4. Clinical relevance of protein domain mutations

### *4.1. Prognostic value of protein domain mutations in cancer patients*

Protein domain mutations have diverse clinical implications in cancer, depending on the type of mutation, the affected protein domain due to mutation, signalling pathways, and the tumor microenvironment. Research suggests that protein domain mutations can potentially be prognostic or predictive biomarkers and treatment responses. For example, the L2 and L3 zinc-binding domains and DNA-binding domain of the TP53 gene are linked to patient poor prognosis and resistance to radiotherapy and chemotherapy in most cancers [116,124]. Similarly, mutations in kinase and helical domains in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) have been found in a variety of malignancies, including breast, ovarian, endometrial, and colorectal cancers, and have been linked to a poor prognosis as well as resistance to immunotherapy and targeted treatments [125]. Individuals with melanoma who have the BRAF kinase V600E mutation respond better to targeted therapies like vemurafenib and dabrafenib. A study of 675 individuals with advanced melanoma showed that those with the BRAF kinase V600E mutation had considerably longer progression-free survival and overall survival than those who did not have this mutation [126]. Mutations in the adenomatous polyposis coli (APC) tumor suppressor gene have been linked to a poor prognosis in colorectal cancer patients. A study on individuals with colorectal cancer showed that those with APC mutations had considerably lower overall survival than those without these mutations [127]. Another example is where mutations in the cyclin-dependent kinase inhibitor 2A (CDKN2A) gene have been linked to a poor prognosis in melanoma. A study of melanoma patients indicated that individuals with CDKN2A gene (protein kinase domain) mutations had considerably lower overall survival than those who did not have these mutations [128,129].

**Table 2**
Reported potential protein domain targets that can act as therapeutic targets (* [58]). protein domains have been predicted as frequently mutated domains and reported in the DCMP database.

| Protein Domain | Target | Function | Reference |
|---|---|---|---|
| BCL-2* | Anti-apoptotic protein | Apoptosis | [191] |
| CDK4/6 | Cyclin-dependent kinases | Cell cycle regulation | [192] |
| EGFR | Epidermal growth factor receptor | Cell proliferation, angiogenesis | [193] |
| FLT3* | FMS-like tyrosine kinase 3 | Cell survival, proliferation | [194] |
| HER2 | Human epidermal growth factor receptor 2 | Cell proliferation, survival | [195] |
| IDH1 | Isocitrate dehydrogenase 1 | Metabolic reprogramming | [196] |
| JAK2 | Janus kinase 2 | Cell proliferation, differentiation | [197] |
| KRAS | Kirsten rat sarcoma viral oncogene homolog | Cell proliferation, survival | [198] |
| mTOR | Mammalian target of rapamycin | Cell growth, metabolism | [199] |
| NTRK | Neurotrophic tyrosine receptor kinase | Cell survival, differentiation | [200] |
| PD-L1 | Programmed death-ligand 1 | Immune evasion | [201] |
| PI3K* | Phosphoinositide 3-kinase | Cell survival, proliferation | [202] |
| PTEN* | Phosphatase and tensin homolog | Tumor suppressor | [203] |
| RAS* | Rat sarcoma viral oncogene homolog | Cell proliferation, survival | [204] |
| RET | Rearranged during transfection | Cell proliferation, differentiation | [205] |
| ROS1 | ROS proto-oncogene 1 | Cell proliferation, survival | [206] |
| SMO* | Oncoprotein Smoothened | Hedgehog pathway signaling | [207] |
| SRC* | Proto-oncogene tyrosine-protein kinase Src | Cell proliferation, survival | [208] |
| TGF-β* | Transforming growth factor-beta | Cell growth, differentiation | [209] |
| TP53* | Tumor protein p53 | Tumor suppressor | [210] |
| VEGF* | Vascular endothelial growth factor | Angiogenesis | [211] |
| AKT | Protein kinase B | Cell survival, proliferation | [212] |
| ALK* | Anaplastic lymphoma kinase | Cell proliferation, survival | [213] |
| BRAF | B-Raf proto-oncogene | Cell proliferation, survival | [214] |
| c-MET | Hepatocyte growth factor receptor | Cell survival, proliferation | [215] |
| DDR2 | Discoidin domain receptor 2 | Cell adhesion, migration | [216] |
| FGFR* | Fibroblast growth factor receptor | Cell proliferation, survival | [217] |
| FLT1 | FMS-like tyrosine kinase 1 | Angiogenesis | [218] |
| HSP90* | Heat shock protein 90 | Chaperone protein | [219] |
| IGF-1R | Insulin-like growth factor 1 receptor | Cell proliferation, survival | [220] |

### 4.2. Predictive values of protein domain mutations for targeted therapy response and resistance

Cancer detection and diagnosis are two distinct types of predictive values. These values can help anticipate cancer in its early stages and after remission and explain patient survival following a cancer diagnosis. It may additionally predict the disease's prognosis after it has been diagnosed. Protein domain mutations can provide predictive value for the responsiveness and resistance of targeted therapies in cancers. The effectiveness of many targeted medicines is based on their ability to block specific proteins or signalling pathways that are frequently disrupted in cancer patients. For instance, mutations at L858R in the kinase domain of EGFR have significant prognostic and predictive consequences in non-small cell lung cancer (NSCLC) [130,131].

In contrast, mutations at C797S and T790 M have shown resistance to EGFR tyrosine kinase inhibitors (TKIs) [132]. In addition, a study that was carried out by Chen et al. found that a mutation site located at R53Q/Q55Pf*29 in the DUF758 domain of tumor necrosis factor alpha-induced protein 8-like 2 (TNFAIP82) was regarded to be a possible predictive marker for tumors such as stomach cancer and colorectal cancer [133]. In addition, a mutation at V600E in the ATP-binding domain of BRAF is regarded as a negative prognostic indicator. This mutation is also associated with resistance to traditional chemotherapeutics, which suggests using a personalized treatment approach in patients with BRAF-mt metastatic colorectal cancer [134]. A comprehensive understanding of the specific mutation and its biological context is required for reliable prediction for the research to show that protein domain mutations can be valuable predictors of therapeutic response and resistance in some circumstances.

Mutations in protein domains can act as biomarkers for both diagnosis and prognosis, as well as guide treatment decisions, identify therapeutic targets, and influence drug resistance (Fig. 3B). There are certain genes, such as ABCB1 or multidrug resistance 1 (MDR1), that are associated with multidrug resistance in cancer. Mutations in transmembrane domain (TMD) such as F72Y, F303Y, I306Y, F314Y, F336Y, and L339Y, as well as nucleotide-binding domain (NBD) (F480Y), can lead to drug resistance [135]. Additionally, mutations in DOT1 domain at R231Q of the DOT1L gene can induce drug resistance in lung cancer [136].

Differentiating between driver and passenger mutations, and managing tumour heterogeneity and resistant clonal populations has posed a significant challenge. It is a well-established fact that proteomic alterations, including post-translational modifications, play a pivotal role in the development of cancer. However, it is noteworthy that proteomics technology has recently attained a level of depth and precision that is comparable to RNA sequencing (Fig. 3A). Promising mass spectrometry-based proteome research that opens the path for clinical use is emphasised. The potential of proteomics and phosphoproteomics to bridge the gap and enable the clinical application of omics analysis is a subject of debate. Comprehending the effects of these domain mutations is crucial in formulating individualised therapeutic approaches and enhancing clinical results within the realm of oncology.

## 5. Challenges and future directions in the use of protein domain mutations as prognostic and predictive biomarkers in cancer

Numerous genetic tests are accessible to detect biomarkers that are associated with particular types of cancer [137]. There are three types of tests that are used to diagnose cancer: cytogenetic tests, gene tests, and biochemical tests [138–140]. Cytogenetic tests involve examining chromosomes for abnormalities that could indicate the presence of cancer [141]. Some cancers are characterized by specific

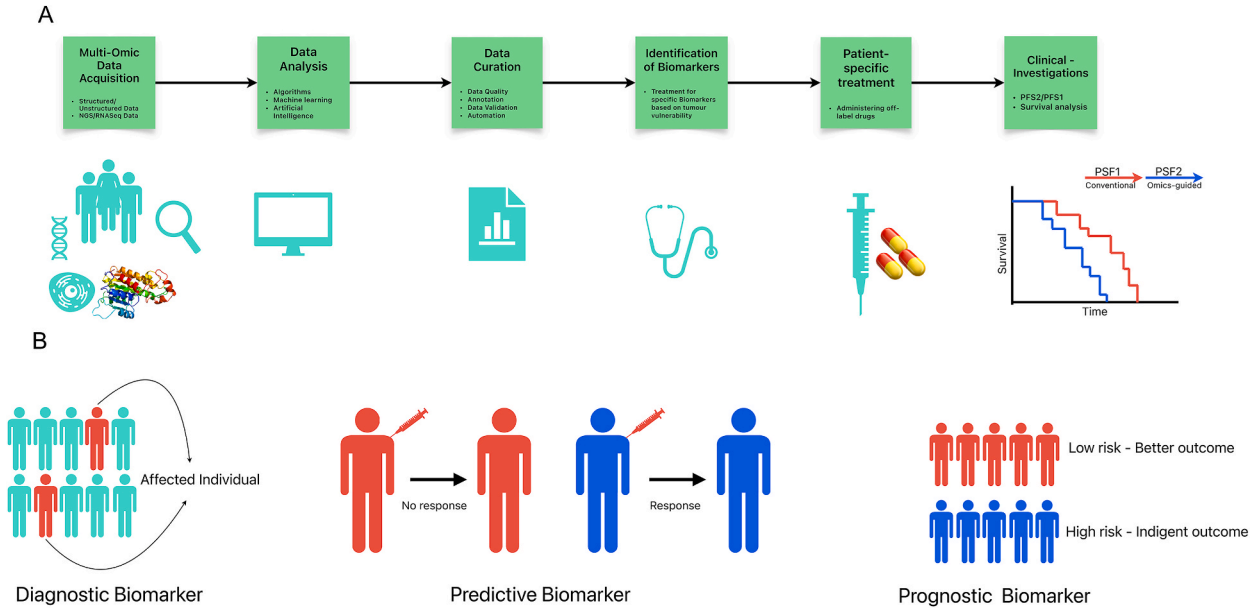


**Fig. 3.** Clinical relevance of protein domain mutation in cancer. A. Flow chart for predicting protein domain as biomarkers from multi-Omics. B. Protein domains can serve as diagnostic and prognostic biomarker in cancer disease.

**Table 3**
List of carcinoma types caused by mutations in protein domains.

| Carcinoma Type | Protein Domain | Function | Target | Ref |
|---|---|---|---|---|
| B-cell leukemia, Lymphoma, Breast cancer, Gastric cancer, Prostate carcinoma, Hepatocellular carcinoma | BCL-2 | Anti-apoptotic protein | Apoptosis | [221] |
| Breast cancer, Lung cancer, Prostate carcinoma, Melanoma, Leukemia, Lymphoma, Glioma, Sarcoma, Colorectal carcinoma, Triple-Negative Breast cancer, Ovarian cancer | CDK4/6 | Cyclin-dependent kinases | Cell cycle regulation | [192] |
| Head and Neck carcinoma, Ovarian cancer, Cervical carcinoma, Bladder cancer, Esophageal carcinoma, Gastric cancer, Breast cancer, Endometrial carcinoma, Colorectal carcinoma, Non-Small Cell Lung cancer | EGFR | Epidermal growth factor receptor | Cell proliferation, angiogenesis | [193] |
| Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Other Hematologic Malignancies, Colorectal carcinoma, Colon carcinoma, Lung cancer, Cutaneous melanoma, Breast Invasive Ductal carcinoma | FLT3 | FMS-like tyrosine kinase 3 | Cell survival, proliferation | [194] |
| Positive Breast cancer, Gastric cancer, Gastroesophageal carcinoma, Bladder cancer, Pancreatic cancer, Ovarian cancer, Stomach carcinoma | HER2 | Human epidermal growth factor receptor 2 | Cell proliferation, survival | [195] |
| Acute Myelogenous Leukemia, Myelodysplastic Syndromes, Brain carcinoma, Oligodendroglioma, Anaplastic Oligodendroglioma, Diffuse Astrocytoma, Cutaneous Squamous Cell carcinoma, Lung cancer, Colorectal carcinoma, Breast cancer, Prostate carcinoma, Thyroid cancer, Cholangiocarcinoma | IDH1 | Isocitrate dehydrogenase 1 | Metabolic reprogramming | [196] |
| Lung adenocarcinoma, Myeloproliferative Neoplasm, Acute Myeloid Leukemia, Breast Invasive Ductal carcinoma, Polycythemia Vera, Colon adenocarcinoma | JAK2 | Janus kinase 2 | Cell proliferation, differentiation | [197] |
| Non-Small Cell Lung cancer, Colorectal carcinoma, Pancreatic cancer, Urogenital carcinoma, Cholangial carcinoma, Ovarian cancer, Endometrial carcinoma | KRAS | Kirsten rat sarcoma viral oncogene homolog | Cell proliferation, survival | [198] |
| Prostate carcinoma, Breast cancer, Lung adenocarcinoma, Colon/Rectum carcinoma, Melanoma, Bladder cancer, Non-Hodgkin lymphoma, Kidney carcinoma, Thyroid cancer, Leukemia, Squamous Cell carcinoma, Ovarian cancer, Renal Cell carcinoma | mTOR | Mammalian target of rapamycin | Cell growth, metabolism | [199] |
| Glioma, Melanoma, Soft-Tissue sarcoma, Inflammatory Myofibroblastic tumors, Congenital Infantile fibrosarcoma, Mesoblastic nephroma, Head and Neck carcinoma, Thyroid cancer, Breast cancer, Cholangiocarcinoma, Colorectal carcinoma, Neuroendocrine carcinoma, Non-Small Cell Lung cancer, Salivary Gland carcinoma, Pancreatic cancer, Appendiceal adenocarcinoma | NTRK | Neurotrophic tyrosine receptor kinase | Cell survival, differentiation | [200] |
| Melanoma, Lung cancer, Breast cancer, Ovarian cancer, Pancreatic cancer, Esophagus adenocarcinoma, Kidney tumors, Bladder cancer, Hematopoietic malignancies, Gastric cancer, Hepatocellular carcinoma, Renal cell carcinoma, Merkle Cell carcinoma | PD-L1 | Programmed death-ligand 1 | Immune evasion | [201] |
| Breast cancers, Colorectal cancer, Gastric cancer, Cervical cancer, Prostate cancer, Lung cancer, Hepatocellular carcinoma, Brain cancer, Endometrial carcinoma | PI3K | Phosphoinositide 3-kinase | Cell survival, proliferation | [202] |
| Glioblastomas, Astrocytoma, Melanoma, Endometrial carcinoma, Colorectal cancer, Breast cancer, Prostate cancer, Non-Small Cell Lung cancer, Head and Neck carcinoma, Mesothelioma, Esophageal cancer, Stomach cancer, Hepatocellular carcinoma, Renal Cell carcinoma, Bladder cancer, Uterine cancer, Cervical cancer, Ovarian cancer, Squamous Cell carcinoma | PTEN | Phosphatase and tensin homolog | Tumor suppressor | [203] |
| Pancreatic ductal adenocarcinoma, Colorectal carcinoma, Non-small cell lung carcinoma, Hematopoietic malignancies | RAS | Rat sarcoma viral oncogene homolog | Cell proliferation, survival | [204] |
| Breast cancer, Salivary gland carcinoma, Papillary Thyroid carcinomas, Adenocarcinoma, Squamous Cell carcinoma, and large cell carcinoma in Non-small Cell Lung cancer, Medullary Thyroid carcinoma, Prostate cancer, Colorectal carcinoma, Pancreatic Cancer, Ovarian cancer | RET | Rearranged during transfection | Cell proliferation, differentiation | [205] |
| Non-Small Cell Lung cancer, Glioblastoma, Cholangiocarcinoma, Ovarian cancer, Stomach cancer, Colorectal cancer, Cutaneous Melanoma, Breast Invasive Ductal carcinoma, Melanoma | ROS1 | ROS proto-oncogene 1 | Cell proliferation, survival | [206] |
| Basal Cell carcinoma, Glioblastoma, Medulloblastoma, Rhabdomyosarcoma, Lung adenocarcinoma, Colon adenocarcinoma, Breast Invasive Ductal carcinoma, Endometrial Endometrioid adenocarcinoma, Cutaneous melanoma | SMO | Oncoprotein Smoothened | Hedgehog pathway signaling | [207] |
| Endometrial cancer, Intestinal cancer, Skin cancer, Colon adenocarcinoma, Breast Invasive Ductal carcinoma, Lung adenocarcinoma, Rectal adenocarcinoma, Cutaneous melanoma | SRC | Proto-oncogene tyrosine-protein kinase Src | Cell proliferation, survival | [208] |
| Colon adenocarcinoma, Ovarian Serous adenocarcinoma, Bladder adenocarcinoma, Oropharyngeal squamous cell carcinoma, Ovarian Endometrioid adenocarcinoma | TGF-β | Transforming growth factor-beta | Cell growth, differentiation | [209] |
| Ovarian Serous adenocarcinoma, Esophageal cancer, Lung adenocarcinoma, Colon adenocarcinoma, Breast Invasive Ductal carcinoma, Pancreatic adenocarcinoma | TP53 | Tumor protein p53 | Tumor suppressor | [210] |

(*continued on next page*)

**Table 3** (*continued*)

| Carcinoma Type | Protein Domain | Function | Target | Ref |
|---|---|---|---|---|
| Endometrial cancer, Intestinal cancer, Skin cancer, colon adenocarcinoma, Lung adenocarcinoma, Breast Invasive Ductal carcinoma, Esophageal adenocarcinoma, Osteosarcoma | VEGF | Vascular endothelial growth factor | Angiogenesis | [211] |
| Breast Invasive Ductal carcinoma, Colon adenocarcinoma, Endometrial Endometrioid adenocarcinoma, Lung adenocarcinoma, Invasive Breast carcinoma, Prostate carcinoma, Bladder Urothelial carcinoma | AKT | Protein kinase B | Cell survival, proliferation | [212] |
| Neuroblastoma, Anaplastic Large Cell lymphoma, Colorectal cancer, Inflammatory Myofibroblastic tumor, Non-Small Cell Lung cancer, Ovarian cancer, Renal Cell carcinoma, Rhabdomyosarcoma, Cutaneous Melanoma, Endometrial Endometrioid adenocarcinoma, Breast Invasive Ductal carcinoma | ALK | Anaplastic lymphoma kinase | Cell proliferation, survival | [213] |
| Melanoma, Non-Small Cell Lung cancer, Colorectal cancer, Papillary Thyroid cancer, Ovarian cancer, Cutaneous melanoma, Lung adenocarcinoma | BRAF | B-Raf proto-oncogene | Cell proliferation, survival | [214] |
| Renal Cell carcinoma, Head and Neck Squamous Cell carcinoma, Childhood Hepatocellular carcinoma, Lung cancer, Gastric cancer, Esophageal cancer, Colorectal cancer, Glioma, Clear Cell Ovarian cancer, Cutaneous melanoma, Melanoma, Endometrial Endometrioid adenocarcinoma | c-MET | Hepatocyte growth factor receptor | Cell survival, proliferation | [215] |
| Lung adenocarcinoma, Breast Invasive Ductal carcinoma, Colon adenocarcinoma, Endometrial Endometrioid adenocarcinoma, Bladder Urothelial carcinoma | DDR2 | Discoidin domain receptor 2 | Cell adhesion, migration | [216] |
| Oral Squamous Cell carcinoma, Breast Invasive Ductal carcinoma, Invasive Breast carcinoma, Esophageal Squamous Cell carcinoma, Ovarian cancer, Bladder cancer, Prostate cancer, Squamous Cell Lung carcinoma | FGFR | Fibroblast growth factor receptor | Cell proliferation, survival | [217] |
| Intestinal cancer, skin cancer, stomach cancer, Lung adenocarcinoma, Colon adenocarcinoma, Cutaneous melanoma, Melanoma, Endometrial Endometrioid adenocarcinoma | FLT1 | FMS-like tyrosine kinase 1 | Angiogenesis | [218] |
| Endometrial cancer, intestinal cancer, Skin cancer, Breast Invasive Ductal carcinoma, Lung adenocarcinoma, Prostate adenocarcinoma, Colon adenocarcinoma, Glioblastoma | HSP90 | Heat shock protein 90 | Chaperone protein | [219] |
| Intestinal cancer, skin cancer, stomach cancer, Breast Invasive Ductal carcinoma, Lung adenocarcinoma, Colon adenocarcinoma, Endometrial Endometrioid adenocarcinoma, Cutaneous melanoma | IGF-1R | Insulin-like growth factor 1 receptor | Cell proliferation, survival | [220] |

changes in chromosomes [142]. Gene tests look for biomarkers like gene duplications, deletions, or mutations [9]. Tissue samples are usually taken for gene tests, but blood tests are becoming more common [143]. Biochemical tests are used to identify abnormal proteins that may be produced by mutated genes. These tests require a tissue sample to identify the proteins [144]. Biochemical tests can also be used to monitor how well a cancer is responding to treatment.

Identification and characterization of mutations in cancer patients may therefore aid in directing personalized treatment options and enhancing patient recovery outcomes [145]. The use of protein domain mutations as cancer biomarkers is not without limitations, and further study is required to get through these problems and access their full potential. The complexity and heterogeneity of cancer present a significant barrier to the application of protein domain alterations as biomarkers. Even within the same type of cancer, considerable heterogeneity in the genetic changes fuelling tumor growth can exist [146]. Various cancer types can exhibit specific genetic and molecular traits [147] (Table 3). As a result, detecting protein domain mutations relevant to a particular cancer subtype or patient population necessitates rigorous genomic and molecular profiling, which can be time-consuming and expensive.

Furthermore, several factors may affect therapy response and clinical outcomes, so even when a relevant mutation is found, it may not necessarily be predictive of these outcomes. Another difficulty is determining the functional significance of protein domain mutations. While some mutations are well-known to provide resistance to specific medicines or enhance tumor growth, many alterations are unknown or have equivocal effects on protein function [148]. Furthermore, the influence of mutation varies depending on the cellular or environmental conditions. As a result, establishing the functional importance of a specific mutation requires extensive experimental validation, which can be difficult in a clinical environment [149,150].

Notwithstanding these limitations, there have been several notable achievements in using protein domain mutations as prognostic and predictive biomarkers in cancer. One such example is mutations in the protein kinase domain of the BRAF gene, implicated in the MAPK/ERK signalling pathway, which has been discovered as predictive indicators for responsiveness to BRAF inhibitors [151]. Furthermore, mutations in the Ras domain that encodes for GTPase of the KRAS gene, implicated in the RAS/RAF/MEK/ERK signalling pathway, are predictive indicators in various cancers, including lung and colorectal cancer, as discussed earlier [152]. Another potential area of research is using protein domain mutations as immunotherapy response indicators. Immunotherapy, which uses the immune system to fight cancer cells, has emerged as a promising treatment method for many types of cancer.

Nevertheless, not all patients respond equally to immunotherapy, so biomarkers that can predict treatment response and guide treatment decisions are required. Many studies have found protein domain alterations linked to immunotherapy response, including mutations in kinase domain at V617F of *JAK1/2*, DNA-binding domain of *TP53* at L22Q, W23S influencing the genes immune checkpoint inhibition (ICI) including *PD-1*, *PD-L1* and *CTLA-4* [153–155]. However, predicting individual responses remains intricate, demanding a comprehensive approach considering multiple biomarkers and the intricate dynamics of the tumor microenvironment.

Further study is needed, however, to validate these indicators and find techniques for incorporating them into clinical practice. Aside from identifying new biomarkers, additional methods and approaches for characterizing protein domain changes and predicting their functional effects are required. Machine learning and other computational tools have shown potential in predicting the impact of mutations on protein structure and function, which could help in the clinical interpretation of genetic data. Furthermore, developments in genome editing tools such as CRISPR/Cas9 have allowed for more efficient and precise experimental validation of mutant functional significance.

Although protein domain mutations hold great promise as prognostic and predictive biomarkers, their successful implementation confronts obstacles relating to data acquisition, functional annotation, validation, and statistics. Future directions include technological advancements, functional studies, combination biomarkers, targeted therapies, real-world evidence, and inter-disciplinary cooperation. Taking on these challenges and investigating these future avenues will pave the way for the effective use of protein domain mutations as biomarkers, resulting in enhanced patient care that is more individualised.

## 6. Discussion

Cancer is a complex disease and thus requires advanced research techniques to identify its underlying causes. Mutation analysis plays a crucial role in identifying the genetic aberrations that lead to malignancy. The application of high throughput sequencing techniques, such as Next-Generation Sequencing (NGS), along with the implementation of hidden Markov models (HMMER), has markedly enhanced mutation analysis. This can offer valuable insights and provide crucial information, such as the genomic location of the mutations, the nucleotide alterations between wildtype and mutated genes, and the type of mutations [156]. Mutations in cancer occur throughout the gene, including non-coding regions, which ultimately impact various cellular processes [157]. And gene regulatory networks (GRNs) that characterize the relationship between genes in a cell are rewired due to gene mutations. Studying such perturbation of GRNs and mutational information becomes crucial during disease prognosis and treatment response, making the mutations important biomarkers for specific phenotypic states [158].

On the other hand, protein domains are functional units of a protein that contribute to the protein's overall structure and functionality. The domain positions are converted into genomic positions using an application programming interface (API) felicitating in mapping the mutations to protein domains [114]. These mutations can provide a more precise understanding of advanced GRNs and specific protein functions that play a critical role in cancer development [159]. Targeting mutations in protein domains associated with different forms of cancer can improve personalized cancer treatment. Identifying these specific mutations is crucial in identifying potential therapeutic targets and revealing fundamental molecular pathways [114,160]. By incorporating mutation analysis and biomarkers into cancer management strategies, clinicians can develop targeted therapies designed to address the specific vulnerabilities arising from protein domain mutations. This not only enhances the treatment efficacy but also minimizes collateral damage to healthy tissues, reducing adverse effects commonly associated with conventional treatments [161].

## 7. Conclusion

Exploring this field further has the potential to improve the diagnosis, prognosis, and treatment of cancer, ultimately leading to better outcomes for patients. Protein domain mutations have shown great promise as biomarkers in cancer; however, their implementation faces some challenges. One significant obstacle is the complexity and heterogeneity of cancer, which makes identifying relevant mutations difficult. Even when relevant mutations are identified, predicting their functional significance and impact on treatment response can be challenging. Additionally, the cost and time required for genomic and molecular profiling can limit the widespread use of protein domain mutations as biomarkers. Finally, determining the functional importance of specific protein domain mutations requires extensive experimental validation, which can be difficult to achieve in a clinical setting. Despite these challenges, protein domain mutations offer great potential for improving cancer diagnosis, prognosis, and treatment outcomes.

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## Data availability

It is a systemic review therefore data is included in the manuscript.

## CRediT authorship contribution statement

**Kiran Kumar Chitluri:** Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Isaac Arnold Emerson:** Writing – review & editing, Supervision, Software, Investigation, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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