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Meta-Analysis of Motor Protein KIF14 with Reference to Cancer

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Abstract
Comprehensive genetic profiling is anticipated to change the way cancer is treatment. KIF14 signaling is responsible for carcinogenesis in a number of malignancies. From this angle, we talk about how often KIF14 mutations and copy number alterations are in different solid tumors. In order to gather information on KIF14 transformation and augmentation from various cancers, we used important data sets such as cBioportal, PubMed, and COSMIC. Our studies describe the clinical data for many malignancies induced by the KIF14 (kinesin family member 14) mutations alter specific regions of the human, Alterations in the KIF14 protein may serve as potential biomarkers for confirming malignant progression. Amino acid and nucleotide variations have been documented across several cancer types. In this review, we provide a comprehensive analysis of these alterations in various malignancies. Our findings indicate that missense mutations are the most prevalent across all cancer types, underscoring the distribution and frequency of KIF14 mutations in different tumor tissues.

Keywords: Receptor threonine kinase, KIF14, Protein regulating cytokinesis 1, Citron kinase, Motor protein, Lung cancer

Introduction

The initial identification of Kinesin was first discovered in 1985 [1]. The group of kinesin superfamily proteins (KIFs) are important microtubule-dependent molecular motors that transport a wide range of cargo, including organelles, transcripts, and proteins, in an ATP-dependent manner [2, 3]. KIF14 is mutated in association with various genes, including ANK2, EGFR, FAT1, GRB2, HGF, KIF2B, MET, MUC17, PAX3, PIK3R1, PTPRT, RYR3, TP53, and TRPA1. Atypical N-3 kinesin family member 14 (KIF1) has been identified as a potential oncogene in several genetic cancers. KIF14 is essential during the late stages of cytokinesis, interacting with protein regulating cytokinesis 1 (PRC1), citron kinase (CIT), and additional regulatory factors to support the proper formation of the cleavage furrow. Despite its well-established role in cell biology, its significance in cancer is increasingly recognized, making KIF14 an intriguing therapeutic target and potential prognostic marker. KIF14 frequently exhibits genomic gain and overexpression in multiple cancers and is located on chromosome 1q32.1, a region commonly amplified in many malignancies [4]. Its expression is tumor-specific and correlates with elevated KIF14 expression has been associated with advanced cancer stages, increased tumor aggressiveness, and poor clinical outcomes in breast, lung, ovarian, liver, and brain cancers. KIF14 further engages with tumor-promoting signaling pathways, enhancing cellular processes such as adhesion, invasion, and resistance to chemotherapy, ultimately contributing to tumor progression. In this article, we summarize the expanding evidence that identifies KIF14 as both a prognostic biomarker and an oncogenic driver across multiple cancer types, and highlight additional findings supporting its potential value as a therapeutic target.

Motor proteins

Motor proteins kinesin and dynein are essential in neuronal function through the conveyance of the various cellular components vesicles, organelles, messenger RNAs, and proteins along microtubules of the axon [5, 6]. These molecular motors harness energy from ATP hydrolysis to generate directional movement along microtubule filaments through discrete stepping motions. A primary function of kinesin family proteins is the transport of cellular cargo from the cell center toward the periphery. The classical form, kinesin-1, is a dimer composed of two heavy chains bound to two light chains. Each heavy chain contains three distinct structural domains: an amino-terminal motor domain, a central coiled-coil domain that mediates dimerization, and a carboxy-terminal tail domain that enables cargo attachment [7].

KIF14 functions:

KIF members are categorized into the N-kinesin, C-kinesin, and M-kinesin subgroups based on the location of their motor domains. According to reports, KIF14 contains four conserved functional domains, including a motor domain required for movement along microtubules via ATP hydrolysis, a fork head associated domain involved in phosphorylation control and includes a stalk domain along with a tail domain responsible for interaction with citron kinase. Numerous biological activities have been associated with the function of KIF14 [8]. This gene encodes a microtubule motor protein belonging to the kinesin-3 superfamily. Kinesin-3 family members are involved in processes

such as moving of vesicles, chromosomal segregation, mitotic spindle formation, and cytokinesis [9, 10]. The microtubule-dependent ATPase activity of the internal motor domain supports its function as a microtubule motor protein. Knockdown of this gene results in multinucleated cells and failed cytokinesis with endoreplication. KIF14 have been recognized as a potential oncogene in breast, lung, and ovarian cancers, and its expression profile suggests it may be a promising therapeutic target. Collectively, clinical, genomic, expression, and functional evidence indicate thatKIF14 is a novel oncogene implicated in the pathogenesis of various cancers [11, 12]. It is an ATPase-activated mitotic kinesin motor protein essential for directing citron kinase to the mitotic spindle through its interaction with protein regulator of cytokinesis 1 (PRC1). Knockdown of KIF14 leads to multinucleation without affecting chromosome segregation. Additionally, KIF14 interacts with supervillin to establish and maintain the cytokinetic furrow [8]. KIF14 has also been reported to interact with β-arrestin 2 within the nucleus of mature spermatozoa. [13].

KIF14 in tumorigenesis

KIF14, which is located on chromosome 1q32, is overexpressed at the genomic and gene expression levels in a number of illnesses, including liver, renal papillary, lung and ovarian tumors as well as breast and retinoblastoma [14] KIF14 is required for cytokinesis' last stage. KIF14, a protein associated with molecular motors and microtubules, was found to have direct interactions with Protein regulating cytokinesis 1 (PRC1) and Citron kinase (CIT), indicating that it plays vital role important organizing role in a cytokinesis [15]. As a result, treatment targets for numerous malignancies that include KIF14-associated gene signaling pathways are therapeutically more significant. The KIF14 has thereby become an interesting therapeutic target. Deregulation of the KIF14 pathway, which can occur in human tumors by a number of mechanisms such as amplification, translocation, point mutations, or overexpression, is what causes malignant transformation and metastasis [16]

Materials and Methods

Databases and patient data

We examined a few open-access public databases, and found that the cBioPortal (http://www.cbioportal.org/public-portal/) and Catalogue of Somatic Mutations (COSMIC) both offer extensive datasets on the human cancer genome. The Cancer Genome Atlas (TCGA; http://cancergenome.nih.gov/) provides full integrated genome data that is available on the cBioportal. The Welcome Trust Sanger Institute's Cancer Genome Project (http://www.sanger.ac.uk/research/projects/cancergenome/), The Cancer Genomics Hub (CGHub; https://cghub.ucsc.edu/), and the International Cancer Genome Consortium (ICGC https://icgc.org/). The National Cancer Institute (NCI; http://www.cancer.gov/) and the National Human Genome Research Institute (NHGRI; https://www.genome.gov/) in particular collaborate on the TCGA, which is publicly accessible. These databases include molecular profiling and the identification of new cancer driver genes. They also contain articles that describe data from large-scale genome screening and imported data from other databases like TCGA, ICGC, etc. In order to search for all clinical cancer data on individuals from cancer studies, including identifying information, mutations, and associated alterations, the KIF14 gene was uploaded to these databases. The National Centre for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov) gene database was used to identify the recognised gene symbols and basic gene activities. We used the biological search engine STRING to examine the cell signalling route. For retrieving interconnected genes and proteins, utilise STRING (http://string-db.org; default mode).

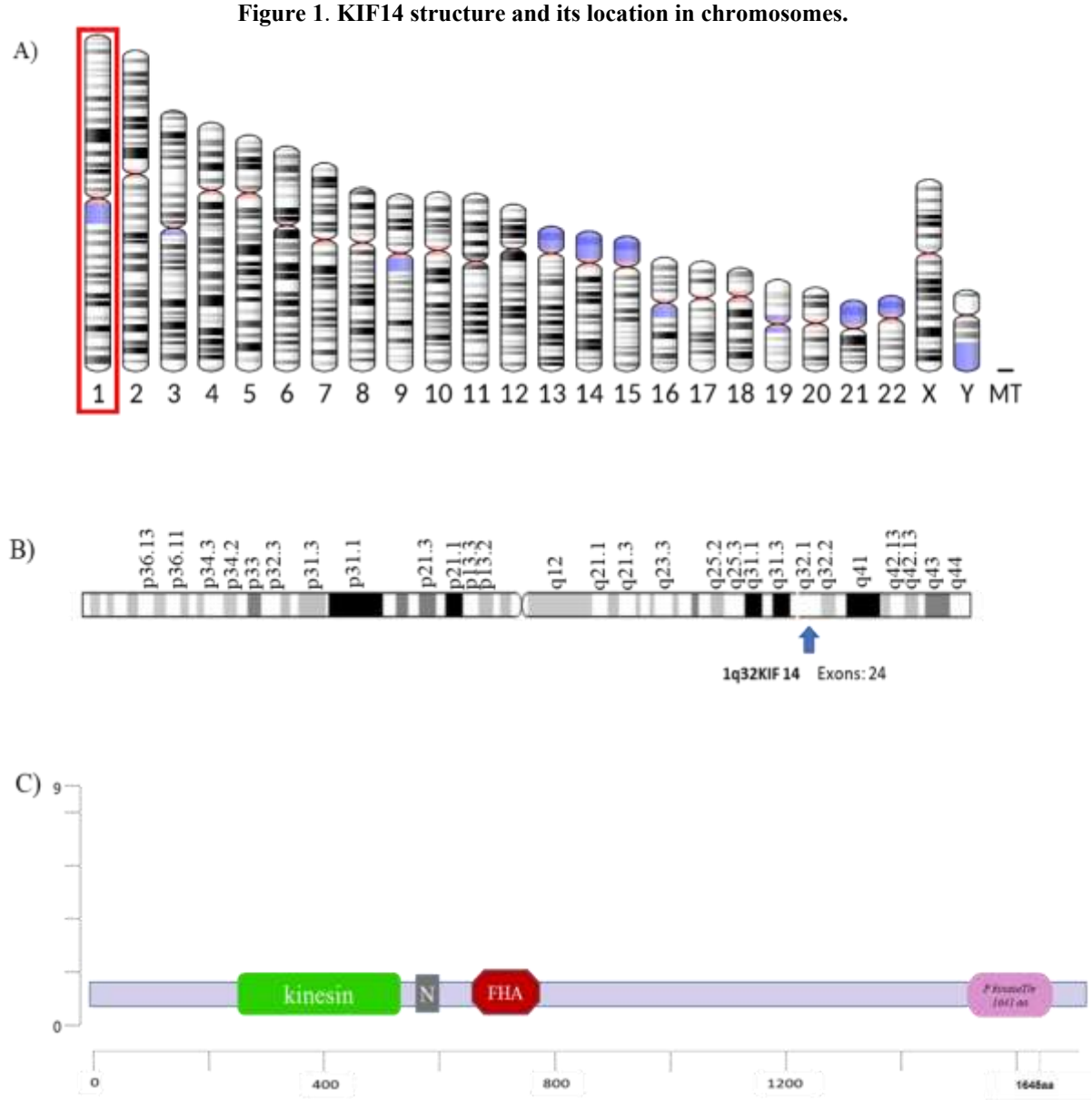
Results

KIF14 mutation analysis from different types of cancer

KIF14 possesses two significant effector domains. The first is a highly conserved kinesin motor domain consisting of 274 amino acids (aa), which contains two microtubule-binding sites: one responsible for ATP-dependent protein transport and the other for microtubule-dependent ATPase activity (aa 447–454). The second is a 67-amino-acid fork head-associated (FHA) domain (aa 825–891), located near the SMAD Mad Homology 2 (MH2) region and associated with proteins that interact with phosphoproteins, although no such interactions have been confirmed for KIF14 to date [17]. In addition to the highly conserved N-type neck region adjacent to the motor domain, KIF14 contains four additional C-terminal regions predicted to form coiled-coil structures (Figure 1). High-throughput studies have identified multiple phosphorylation (P) sites at Ser-12, Tyr-196, Thr-240, Ser-, as well as a ubiquitination (U) site at Lys-275. The N-terminal extension (354 aa) plays a crucial role in interacting with PRC1 (protein regulating cytokinesis 1), whereas citron kinase binds to the C-terminal stalk and tail of KIF14. Supervillin interacts directly with the distal C-terminal tail (aa 1522–1648), while Radil associates with the terminal four amino acids (aa 1645–1648) [45]. The interaction between the N-terminal extension and PRC1 is essential for proper formation of the central spindle during cytokinesis. The association between citron kinase and the C-terminal stalk-tail region is required for accurate localization of KIF14 to the mitotic spindle. Additionally, supervillin, a membrane-associated protein involved in regulating cell motility, has been shown to interact with the distal C-terminal tail of KIF14 and contributes to the establishment or maintenance of the cytokinetic furrow [8]. Mutations in KIF14 were analyzed using cBioPortal and COSMIC across multiple cancer types, including adrenal gland cancer, cholangiocarcinoma, bladder urothelial carcinoma, colorectal cancer, breast cancer, central nervous system/brain tumors, cervical cancer, stomach cancer, head

and neck cancers, liver cancer, pancreatic cancer, ovarian cancer, soft tissue cancers, thyroid cancer, and endometrial cancer. These datasets comprise 188,323 samples from 179,879 patients across 373 studies. Of these samples, 2,857 (approximately 2%) contained KIF14 mutations. Structural predictions were referenced using the KIF14 AlphaFold Protein Structure Database, alongside comparisons with kinesin family proteins (Kinesin-1 through Kinesin-14A&B Figure 2 & 2B.

Figure 1. **KIF14 structure and its location in chromosomes.**



(A) shows 24 chromosomes including sex chromosomes and the first chromosome was highlighted. (B) A first chromosome and the arrow mark point out the KIF14 gene position within the chromosome. (C) KIf14 protein structure. Kinesin domain; N-Terminal; FHA-forkhead-associated domain; Pkinase- Thr, Threonine kinase catalytic domain; AA, amino acid.

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Figure 2 KIF 14 AlphaFold Protein Structure Database

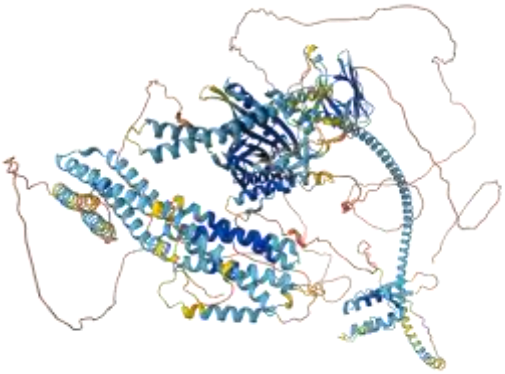
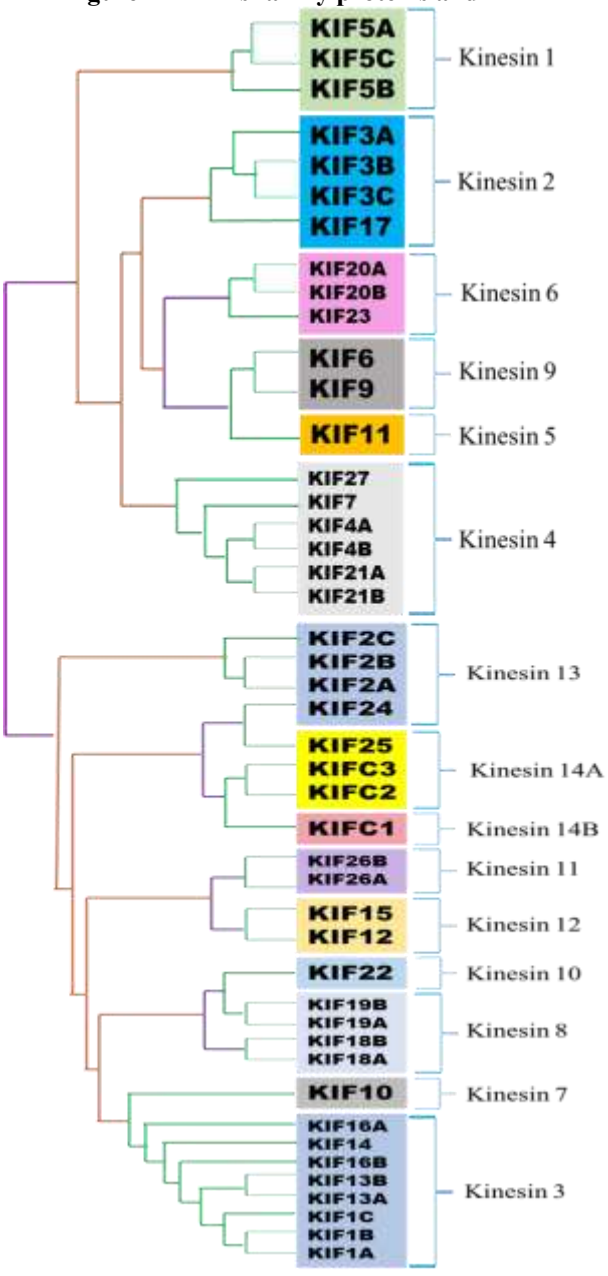


Figure 2B KIF's family proteins and KIF14



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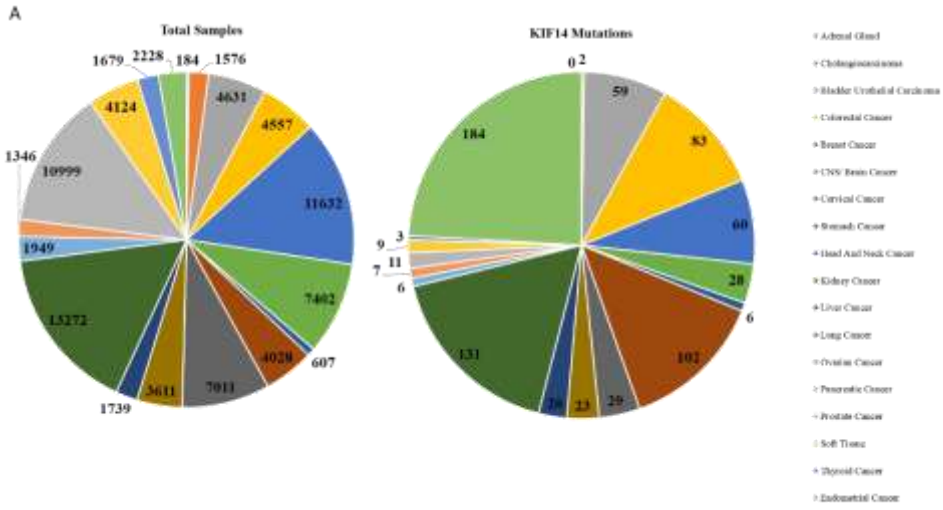
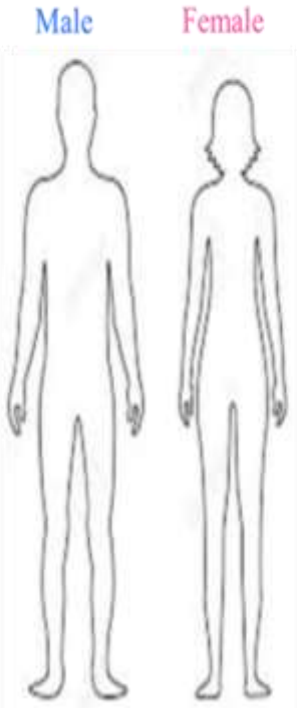
The table shows various cancer types and their corresponding sample sizes. Notably, lung cancer has the highest number of analyzed samples (13,272), within which KIF14 mutations were identified, followed by breast cancer with 11,632 cases and 11,091 mutations (Figure 3). Other cancer types exhibit comparatively lower frequencies of KIF14 mutations. Based on patient data, gender-wise analysis revealed that males are more frequently affected by cancers harboring KIF14 mutations than females. Several gender-specific cancers also demonstrated KIF14 mutations, including bladder cancer (2,944 cases) and prostate cancer (8,412 cases) in males, and breast cancer (10,851 cases), endometrial cancer (1,948 cases), and ovarian cancer (1,132 cases) in females. Overall, lung and breast cancers show the highest prevalence of KIF14 mutations in both sexes. However, a substantial portion of patient history data is either missing or unavailable in the database. For KIF14-mutated cancers, clinical characteristics such as sex, age, race, smoking status, histology, and performance or living status were examined, but the completeness of these data remains limited. Among the available records, individuals identified as White were the most affected by KIF14 mutations, followed by African, Asian, and other racial groups. Table 1.

Figure 3. KIF14 mutation analysis from various cancer types.



B

Adrenal gland	64	Adrenal gland	120
Cholangio carcinoma	712	Cholangio carcinoma	587
bladder urothelial carcinoma	2944	bladder urothelial carcinoma	993
colorectal cancer	2172	colorectal cancer	2073
breast cancer	0	breast cancer	10851
CNS/ Brain cancer	3730	CNS/ Brain cancer	2562
cervical cancer	0	cervical cancer	604
stomach cancer	2838	stomach cancer	1038
Head and neck cancer	4373	Head and neck cancer	2054
kidney cancer	1856	kidney cancer	1162
Liver cancer	1023	Liver cancer	386
Lung cancer	5274	Lung cancer	5608
ovarian cancer	0	ovarian cancer	1127
pancreatic cancer	732	pancreatic cancer	593
prostate cancer	8412	prostate cancer	2
soft tissue	1851	soft tissue	2021
thyroid cancer	436	thyroid cancer	1132
endometrial cancer	0	endometrial cancer	1948



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A) The pie chart circle shows the total number of samples examined for each cancer's KIF14 mutation, and the inner circle depicts the number of KIF14 mutations found in the various tissue types. In contrast, these three cancers Endometrial cancer with mutation 182 found in 2228 samples, lung cancer with mutation 131 found in 13272 samples, and stomach cancer with mutation 102 found in 4028 samples are highly mutated with KIF14. B) Male and female KIF14 mutation frequencies; clinical data from male and female KIF14 mutation cancer patients of various types; The numbers indicate the number of KIF14 mutations on specific cancer tissue in males and females, respectively (male 5274 and female 5608). Male lung cancer is primarily affected by KIF14, while female breast cancer has 10851 mutations.

Tumour characteristics of various cancer

Table 2 provides a summary of the characteristics of the tumor and Table 3 Copy number variations (CNVs) involving KIF14 amplification have been observed in various cancer tissue types. Research has shown that CNVs play a crucial role in cancer development and progression, with KIF14 being implicated in these genomic alterations [12, 34]. Studies have highlighted the significance of CNV analysis in identifying clinically relevant gene amplifications that can guide treatment selection, emphasizing the need to incorporate CNV testing into routine next-generation sequencing (NGS) analyses for uncovering actionable targets in cancer therapy [35]. Furthermore, deep learning models have been developed to classify different cancer types based on CNV data, showcasing the potential of advanced computational techniques in understanding the genomic landscape of cancers and identifying specific alterations like KIF14 amplifications. Additionally, the analysis of CNVs

Table 1. Summary of patient's history and tumor clinical characteristics of KIF14 mutated various cancer types

Patient characteristics	Adrenal gland	Cholangio carcinoma	Bladder urothelial carcinoma	Colorectal cancer	Breast cancer	CNS/ brain cancer	Cervical cancer	Stomach cancer	Head and neck cancer	Kidney cancer	Liver cancer	Lung cancer	Ovarian cancer	Pancreatic cancer	Prostate cancer	Soft tissue	Thyroid cancer	Endometrial cancer
Total sample	184	1576	4631	4557	11632	7402	607	4028	7011	3611	1739	13272	1949	1548	10999	4124	1679	2228
nos	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Male	64	712	2944	2172	0	3730	0	2838	4373	1856	1023	5274	0	732	8412	1831	436	0
Female	120	587	993	2073	10851	2562	604	1038	2054	1162	386	3688	1127	593	2	2021	1132	1948
NA	0	274	187	152	0	651	1	87	423	516	250	537	765	21	2166	210	52	270
Total Mutation count	181	1468	4522	4022	11091	3906	483	3977	6897	3327	1727	13272	1413	1233	10651	4118	1508	1760
KIF14 mutation	0	2	59	83	60	28	6	102	29	23	20	131	6	7	11	9	3	184
mRNA expression	157	72	1648	1080	3436	1706	600	1469	1316	2232	739	2401	1047	334	1324	1073	1489	1151
White	156	230	2702	585	0	2029	414	1254	1004	2073	459	3864	936	405	0	0	981	853
Black	2	7	149	193	0	162	58	34	93	13	34	293	87	3	0	0	74	230
Asian	4	6	183	24	0	43	48	375	23	37	342	208	37	22	0	0	153	44
Other	0	0	27	0	0	0	0	21	2	9	9	112	0	0	0	0	27	0
Structural variants	91	837	2812	2208	4704	2318	291	68	2081	1446	666	11078	610	184	8545	3272	1031	879
Histology (NA)	0	1112	3951	3818	0	3862	0	1201	0	0	122	426	0	0	168	0	0	2047
Adenocarcinoma	0	0	0	440	0	0	0	0	0	0	0	10353	0	1164	10346	0	0	0
Squamous cell carcinoma	0	0	0	0	0	0	0	0	1444	0	0	2028	1	0	1	0	0	0
Lung	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Other	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Living	116	402	1961	2463	3397	0	464	1881	2809	2296	729	4189	692	252	2307	2542	1439	1333
Deceased	67	795	1325	1038	2101	0	140	1237	1371	703	456	2477	1000	214	608	1208	190	336

The sex, age, race, tumor histology, and patient performance status of various cancer tissues is displayed in the KIF14-mutated patient history data in the table. In contrast, the majority of cancers have mean ages above 50, with a few cancers having mean ages below 50. In the race category, white people are highly affected by the KIF14 mutation specifically in lung cancer (3864), Bladder urothelial carcinoma (2702), and kidney (2073) followed by the Black, Asian, and other categories.

Table 2. Summary of the KIF14 mutated cancer with clinical characteristics of tissue type and its stage

Cancer types	Tumour types		Stage								
	Primary	Metastasis	NA	I	I A &B	II	II (A&B)	III	III A, B&C	IV	IV A&B
Adrenal gland	184	0	0	0	0	0	0	0	0	0	0
Cholangio carcinoma	432	190	1341	44	0	86	0	56	0	0	135
Bladder urothelial carcinoma	3253	393	898	0	0	0	0	0	0	0	0
Colorectal cancer	2443	757	1338	12	0	42	1	48	0	36	0
Breast cancer	0	249	11113	11	0	73	0	19	0	0	0
CNS/ Brain cancer	4091	2	2376	0	0	0	0	0	0	0	0
Cervical cancer	605	2	0	0	0	0	0	0	0	0	0
Stomach cancer	2996	272	760	0	0	0	0	0	0	0	0

Head and neck cancer	1939	172	858	0	5	6	3	0	37	47	0
Kidney cancer	2316	0	1295	9	0	2	0	31	0	8	0
Liver cancer	856	16	861	0	0	0	0	0	0	0	0
Lung cancer	5447	4535	3699	181	657	105	339	115	153	68	0
Ovarian cancer	1715	83	131	0	0	0	0	0	0	0	0
Pancreatic cancer	745	4	598	0	8	0	14	0	0	0	0
Prostate cancer	0	0	0	0	0	0	0	0	0	0	0
Soft tissue	0	0	0	0	0	0	0	0	0	0	0
Thyroid cancer	1595	28	0	268	0	49	0	102	0	2	39
Endometrial cancer	1606	66	555	0	31	0	0	0	6	0	1

Tumors are categorized into two types: primary and metastatic. Comparatively, primary tumor samples were more frequently analyzed for KIF14 mutations, while only a limited number of metastatic tumor tissues were examined. Staging data indicate that KIF14 mutations are most commonly observed in stage II, III, and IV tumors across multiple cancer types. The numbers represent the sample counts within each cancer category.

Table 3 Summary of Copy number variations (CNVs) data of various cancers

Cancer types	**Total number of cases across the study**	**cases with CNV & Gain: Loss**	**Gender (M/F)**	**Mean age**
Adrenal gland	184	-	-	-
Cholangiocarcinoma	36	1 & 4:0	-	-
Bladder urothelial carcinoma	5276	36 & 36:0	FM16 & M20	63.2
Breast	1492	100 & 99:0	F100	45
CNS/ Brain	1035	1 & 1:0	M1	53
Cervical	299	3 & 3:0	FM3	53
Stomach	472	1 & 1:0	M1	64
Head and neck	2983	3 & 3:0	M2	60
Kidney	995	1 & 1:0	M1	53
Liver	663	24 & 24:0	FM13& M11	64
Lung	1006	15 & 15:0	FM6 & M9	67.5
Ovarian	684	5 & 5:0	FM5	61.5
Pancreatic	898	1 & 1:0	FM1	64
Prostate	2079	46&40:0	M68	68
Soft tissue	264	1 & 1:0	-	-
Thyroid	490	2 & 2:0	FM2	76.5
Endometrial	586	15 & 15:0	FM15	50

Copy number variations (CNVs) play a major role in cancer development, with gains being more prevalent than losses in the analyzed tumor samples. The data also indicates that males exhibit higher CNVs compared to females, and the mean age across various cancers is typically above 50 years. Moreover, the analysis of minor intron splicing in different cancer cohorts suggests context-dependent roles of the minor spliceosome in tumorigenesis, paving the way for further investigations into minor splicing in cancer and potential therapeutic strategies. These findings collectively underscore the significance of CNVs, gender disparities in CNV frequencies, and age-related patterns in cancer development.

formalin-fixed paraffin-embedded (FFPE) cancer samples has revealed varying frequencies of CNVs across different cancer types, shedding light on the diverse genomic profiles and alterations present in melanoma, non-small cell lung cancers (NSCLC), and colorectal cancers (CRC), including amplifications in druggable targets like BRAF, EGFR, and KRAS [36]. The patient's outcome is linked to the type and stage of cancer. The KIF14 mutation was looked for in several primaries and some metastatic tumor samples. Stage analysis of a tumor reveals that most samples in the first, second, and third stages have a higher KIF14 mutation, with a few samples in the first stage also having the mutation. In this analysis, we undertook a scrutiny of the tissue-specific distribution of multiple KIF14 mutation types across

disparate cancer types (Table 4). In summary, our findings indicated that missense mutations are predominantly observed in the skin (107), lung cancer (84), and large intestinal cancer (70), as well as in virtually all other cancer forms, with the exceptions of endometrial and gastric cancers, along with a few others. Conversely, mutations such as nonsense, insertion, deletion, synonymous, and nonsynonymous mutations exhibited minimal prevalence across all cancer types Table 4. In this study, we conducted a tissue-specific distribution analysis of various KIF14 mutations found in various cancers. Table 6 provides a summary of the most recent clinical investigation concerning patients with KIF14 alteration, including their clinical characteristics, treatment modalities, and outcomes across various types of cancer. The presence of KIF14 mutation and increased expression levels was predominantly observed in advanced stages of all cancer types, thereby suggesting a significant association between c-Met alteration and the progression of tumors.The Oncomine database expression analysis of KIF14

Table 4 Multiple variations of KIF14 mutations in tissue-specific malignancies.

Cancer types	Nonsense	Missense	Synonymous	Insertion	Deletion	Others
Adrenal gland	0	0	0	0	0	0
Cholangiocarcinoma	4	0	0	0	0	0
Biliary tract	0	5	2	0	0	7
Bladder urothelial carcinoma	2	21	11	0	0	1
Breast cancer	1	22	6	0	1	2
CNS/ Brain cancer	1	29	3	0	0	5
Cervical cancer	1	1	4	0	0	0
Endometrium	4	68	10	1	0	3
Stomach cancer	1	45	4	3	2	2
Head and neck cancer	2	29	7	0	0	0
Kidney cancer	0	14	0	1	0	0
Large intestine	6	70	18	3	8	7
Liver cancer	1	21	11	0	0	7
Lung cancer	2	84	17	0	0	7
Ovarian cancer	1	3	1	0	0	1
Pancreatic cancer	0	8	1	0	0	7
Prostate cancer	1	5	6	0	0	0
Soft tissue	0	12	0	0	0	2
Thyroid cancer	1	16	2	0	0	0
Skin	10	107	20	1	1	3

revealed that, when compared to the adjacent tissues of various cancers, including LUAD (Lung adinocarcinoma), KIF14 was over expressed. The results of differential expression analysis through The Cancer Genome Atlas (TCGA) database confirmed that KIF14 was upregulated not only in LUAD but also in uterine corpus endometrial carcinoma (UCEC), thyroid carcinoma (THCA), stomach adenocarcinoma (STAD), Sarcoma (SARC), rectum adenocarcinoma (READ), prostate adenocarcinoma (PRAD), pancreatic adenocarcinoma (PAAD), lung squamous cell carcinoma (LUSC), liver hepatocellular carcinoma (LIHC), kidney renal papillary cell carcinoma (KIRP), kidney renal clear cell carcinoma (KIRC), head and neck squamous cell carcinoma (HNSC), glioblastoma multiforme (GBM), esophageal carcinoma (ESCA), colon adenocarcinoma (COAD), cholangiocarcinoma (CHOL), endocervical adenocarcinoma (CESC), breast invasive carcinoma (BRCA), cervical squamous cell carcinoma (CESC), and bladder urothelial carcinoma (BLCA) were included in the analysis. In terms of base-pair substitution, liver and lung tissues showed the highest mutation counts across all cancer tissue datasets. In liver tissue, 154 base-pair changes were detected, with A > G (34) and G > A (32) substitutions being the most frequent. In lung tissue, 110 base-pair changes were identified, with G > T (22) and A > G (19) substitutions occurring most frequently. Conversely, tissues such as the salivary gland, genital tract, small intestine, and placenta exhibited lower base-pair alterations compared to other cancer tissues (Figure 4). Across all tissues, minimal single base-pair substitutions were observed, including C > T (1), G > A (2), and G > T (1). To improve our understanding of KIF14 alterations, we examined amino acid (AA) substitutions across various cancers. Notably, lung cancer displayed higher alterations in alanine (A) (4), cysteine (C) (5), glutamic acid (E) (4), lysine (K) (5), leucine (L) (9), methionine (M) (6), serine (S) (8), valine (V) (6), and tryptophan (W) (1). Aspartic acid (D) (4) was frequently altered in stomach cancer, phenylalanine (F) (4) in thyroid cancer, and in endometrial cancer, alterations were observed in glycine (G) (3), isoleucine (I) (11), lysine (K) (5), asparagine (N) (6), glutamine (Q) (7), arginine (R) (4), and threonine (T) (7). Histidine (H) (8) was highly altered in large intestine cancers, while arginine (R) (4) and tyrosine (Y) (5) were elevated in stomach cancer. Overall, isoleucine (I) substitutions were found in approximately 10% of cases, followed by arginine (R) (8%), threonine (T) (8%), serine (S) (7%), histidine (H) (7%), and lysine (K) (7%). Alterations in leucine (L), asparagine (N), and glutamine (Q) were observed in 6% of cases, while the remaining amino acids exhibited mutation frequencies of 5% or less (Figure 5). Proteins consist of distinct extracellular and intracellular regions known as domains. We observed that certain regions of KIF14 were repeatedly or

highly mutated, forming mutation hotspots (Figure 6). In particular, the kinesin motor domain and protein kinase-associated regions were highly mutated across most cancers, suggesting that these regions serve as the primary focal points for KIF14 alterations. However, additional domains also displayed minor mutation frequencies. Overall, the results indicate that mutations can occur throughout the entire KIF14 protein. Potential mechanisms involved in tumorigenesis are influenced by the interacting partners within the KIF14 signaling network. Search Tool for the Retrieval of Interacting Genes/Proteins is a network analysis database that depicts physical and functional protein–protein interactions. We used STRING to visualize the interaction network associated with KIF14 (Figure 7), and the names and functions of the interconnected genes are summarized in Table 5. However, most KIF14 mutations and elevation in expression are seen during late-stage cancer, further indicating that KIF14 changes are linked to tumor progression. The combined datasets were analyzed to analyze copy number alterations (CNAs) and survival outcomes to identify significant associations between motor proteins and cancer. CNAs were isolated in 47%, 49% and 57% of the patients, respectively, that belonged to at least one kinesin, dynein and myosin family member. Survival analysis showed that CNAs belonging to the kinesin and dynein families were found to be significantly related to lower overall survival. These observations add to an accumulating body of knowledge demonstrating motor proteins as future therapeutic targets in cancer. Kinesin inhibitors can block spindle assembly or centrosome separation in mitosis to prevent cell cycle progression and result in apoptosis [18]. Kinesins have been reported to be overexpressed or underexpressed in different cancers, indicating different functions of different family members. For instance, KIF14 is overexpressed in breast cancer and several retinoblastomas, indicating its oncogenic activity [19]. By contrast, KIF14 acts as a tumor suppressor and metastasis inhibitor in lung adenocarcinoma.[20].

Discussion

We investigated the effect of KIF14 mutations among several cancer types. We obtained all data from two very large open-access databases, analyzing 763 mutations of KIF14 from 82,575 samples of tumors. Analysis of tumor stages revealed higher frequency of advanced metastatic stages in lung cancer (4,535 samples) and colorectal cancer (757 samples), bladder urothelial carcinoma, stomach cancer, and breast cancer. However, stages I and IA/IB had the highest number of patients of all cancers. Results from other researches have demonstrated that late-stage patients with cancer have generally worse prognosis overall. National and international guidelines suggest these genetic changes can be seen in any patient regardless of race, age, sex, or survival outcomes. Table 1 presents patient demographics, including gender, race, age distribution, tissue histology. Network analysis has evolved an excellent tool to explore complexity of bio-interaction, specifically protein–protein interaction networks, which give clues to cancer-related cellular phenotypes. Some proteins are essential for cytokinesis and influence cancer progression and patient status, including PRC1 (Protein Regulator of Cytokinesis 1), KIF14 (Kinesin Family Member 14), and CIT (Citron Rho-interacting Serine/Threonine Kinase). This project aimed at finding out the prognostic value of PRC1, KIF14 and CIT in colorectal and pancreatic cancer [21]. Indeed, in line with the established clinical risk factors alone, we report the first proof that KIF11 protein and mRNA, and KIF14 mRNA can help distinguish colorectal cancer patients (colon and rectum) with more favorable prognosis [22]. Low expression of KIF11 or KIF14 in these tumors was positively correlated with enrichment of circadian-clock-related tumor gene sets and high expression positively correlated with genomic instability-related tumor gene sets. Level of KIF11 and KIF14 expression showed positive correlation and CEP55, ASPM and GAMT were revealed to be central hub genes [12]. Anillin (ANLN), the most ubiquitous actin-binding protein, regulates cell growth, migration and cytokinesis. Numerous studies have described the upregulation of ANLN in different cancers and associated it with poor tumor prognosis and aggressive activity. In contrast, our study showed a positive relationship of expression of ANLN with cell cycle control, nucleocytoplasmic transport and Fanconi anaemia pathway. In addition, expression of ANLN was significantly correlated with KIF14, DEPDC, KIF23, RACGAP1, and CKAP2L in all cancer types. [23].

Table 5. KIF14-interlinked genes and their function in normal cell regulation

Genes	Genes and their functions in cell
ANLN	Anillin, Actin Binding Protein; During cytokinesis and cellularization, anillin, a conserved protein, is thought to play a significant in the dynamics of the cytoskeleton.
ASPM	Abnormal spindle-like microcephaly-associated protein, Instructions for making a protein involved in cell division are provided by the ASPM gene.
AURKB	Aurora kinase B, It is a component of the complex of chromosomal passenger proteins and participates in the advancement of the cell cycle.
BIRC5	Baculoviral IAP repeat containing 5; It is a prognostic biomarker related to growth invulnerable cell invasion.
BUB1	Budding uninhibited by benzimidazoles 1; The protein is bound to kinetochores and assumes a critical part in the foundation of the mitotic shaft designated spot and chromosome congression.
CDCA8	Cell division cycle associated 8; It has been notable as a cell cycle controller and cancer promotor in different dangerous growths.
CENPA	

	Centromere protein A; It is a protein that epigenetically characterizes the place of the centromere on every chromosome, deciding the place of kinetochore gathering and the last site of the sister chromatid union during mitosis.
CENPF	Centromere Protein F; Throughout the interphase's G2 phase, the protein is a part of the nuclear matrix. The protein forms an association with the kinetochore in late G2 and continues to do so through early anaphase.
CEP55	Centrosomal protein of 55 kDa; During cytokinesis, the 55 kDa centrosomal protein plays a crucial role in membrane abscission.
CIT	citron rho-interacting serine/threonine kinase; CIT-K is an essential abscission regulator that may enhance midbody stability through active RhoA and anillin.
DLGAP5	Disks large-associated protein 5; It has a remarkable capability in settling shaft development and getting through microtubule attacks from docetaxel, in an androgen-directed cell cycle framework.
EGFR	Epidermal growth factor receptors; The gene encoding the protein that traverses the cell membrane is called the epidermal growth factor receptor (EGFR). The protein's other ends stick out from the cell's surface while the other end remains inside the cell.
INCENP	Inner centromere protein; After cytokinesis, the proteins are discarded in the midbody of the cell in the intercellular bridge during telophase.
KIF11	KIF11 is an individual from the kinesin superfamily, which are nanomotors that move along microtubule tracks in the cell.
KIF14	Kinesin-like protein; By binding to, crosslinking, or moving microtubules, the kinesin-14 motor family members of the kinesin-14 motor family can control microtubule arrangement and spindle assembly.
KIF20A	Kinesin Family Member 20A; Engaged with microtubule pack development; mid-body amputation; and controlling cytokinesis. Located in a number of parts of the cell, including the cleavage furrow; intercellular extension; and midsection
KIF2C	Kinesin-like protein 2C; This ATP-dependent MT depolymerization factor is required for spindle assembly, MT dynamics, correct kinetochore-MT attachment, and chromosomal placement and segregation.
MAD2L1	Mitotic spindle assembly checkpoint protein; The mitotic shaft assembly designated point is what delays the start of anaphase until all chromosomes are properly positioned at the metaphase plate.
PLK1	Polo-like kinase 1; Plk1 is a serine/threonine protein kinase that assumes various basic parts in centrosome development, mitotic chromosome isolation, cytokinesis, and the DNA harm reaction.
PRC1	Protein Regulator of cytokinesis 1; contributes to the spindle's proper formation during the metaphase. Central spindle organization and midzone formation are essential functions of kinesin family member 4 and its binding partner, PRC1.
TP53	Tumour protein 53; A characteristic that gives rise to a protein that is found deep inside cells and has a significant role in regulating cell division and cell migration. The body may grow and spread cancer cells due to TP53 mutations (changes).
TTK	Threonine tyrosine kinase; This quality encodes a double particularity protein kinase with the capacity to phosphorylate tyrosine, serine, and threonine. Related to cell multiplication, this protein is fundamental for chromosome arrangement at the centromere during mitosis and is expected for centrosome duplication.

This table lists 23 genes with information relating to the KIF14 protein action network. The table includes gene symbols with an explanation and significant roles in cell signalling.

On the other hand, KIF14 functions as a tumor suppressor and metastasis inhibitor in lung adenocarcinoma. KIF20A is overexpressed in pancreatic cancer, while KIF10 is under expressed in hepatocellular carcinoma. Inhibition of certain kinesins has been reported to reduce cancer cell motility. For instance, inhibition of KIF20A was shown to decrease the motility of bladder cancer cells [19, 24].. Two distinct classes of midbody proteins were identified: **transient** midbody proteins—such as Anillin, Aurora B, and PRC1—which rapidly accumulate at the midbody after the onset of anaphase and gradually disappear; and **stable** midbody proteins—such as CIT-K, KIF14, and KIF23—which persist at the midbody throughout cytokinesis and remain even after abscissio [25].

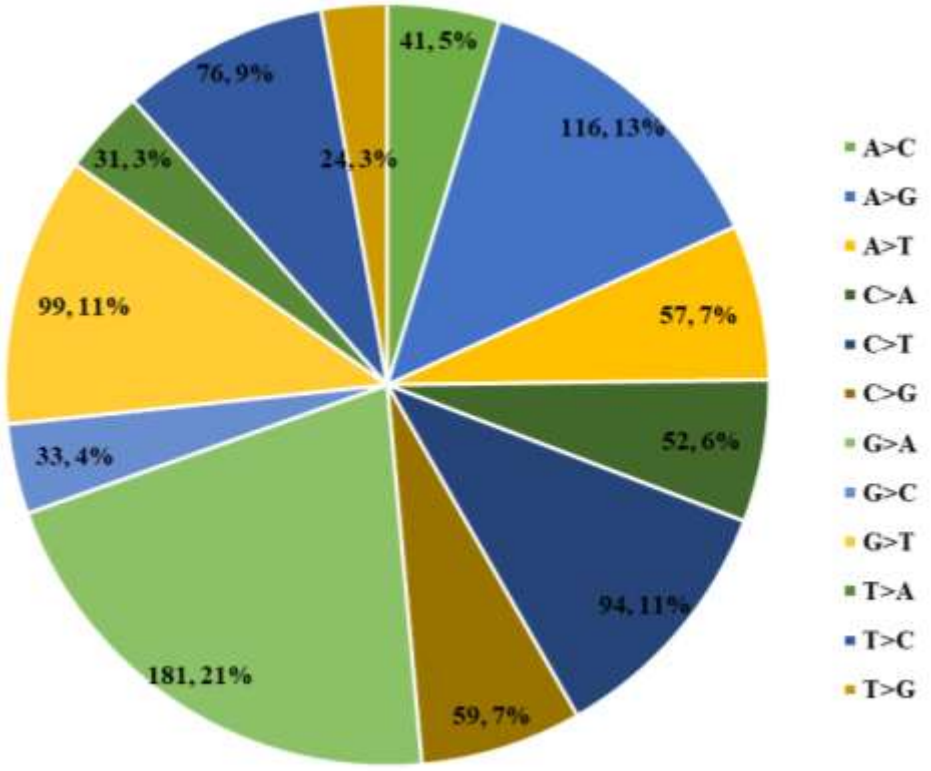
Table 6 Summary of KIF14 mutation & Expression survival status, and other patient's clinical characteristics

Primary tissue and histology subtype	Patients	Mutation types & expression	Drugs name	Race Gender M/F	Age years	Smoking status	Survival Status	Other genes mutations in same case or study	References
cholangiocarcinoma	17	NA	NA	M – 12 FM - 5	49 - 78	NA	24 Months	Identified recurring alterations in previously identified genes such as KRAS, TP53, APC, as well as in genes regulating epigenetics.	Kim et al., 2016 [37]
Colorectal cancer	31	somatic mutations were identified in the genes responsible for DNA-proofreading or mismatch repair, namely POLE, MLH1, and MSH6, leading to a hypermutable phenotype in the tumor cells.	NA	NA	NA	NA	NA	TP53 was the most commonly	Robles et al., 2016 [38]
Cholangiocarcinoma (CCA)	NA	KIF14 exhibited increased expression levels in cholangiocarcinoma (CCA) specimens, particularly in individuals with lymph node metastasis and vascular invasion.	Gemcitabine based chemotherapy-resistance	NA	NA	NA	CCA patients with higher KIF14 were associated with worse overall survival and recurrence-free survival after surgery.	NA	Jiang et al., 2023 [39]
Gastric cancer	90	Ectopic overexpression	NA	67 men and 23 women	34 to 83 years of age	NA	NA	In addition to KIF14, numerous other members of the kinesin family have been identified as genes that promote tumor	Yang et al., 2019 [40]

								growth, such as KIF3A, KIF5B, KIF1B, KIF4A, KIF7, and KIF2a.	
Pancreatic Adenocarcinoma	68	KIF14 exhibited high levels of expression in pancreatic ductal adenocarcinoma (PDAC) cells that showed no invasion of nerves, but its expression was reduced in cells that did invade nerves. Additionally, KIF14 was downregulated in non-invasive compared to neuroinvasive cell lines of pancreatic carcinoma.	NA	NA	NA	NA	2 years	CEP55, ASPM, and GAMT were identified as the primary central nodes, demonstrating close association with KIF11 and KIF14 within the protein interaction network of PAC.	Klimaszewska-Wiśniewska et al., 2021 [41]
Lung adenocarcinoma	466	The expression of KIF14 is predictive of disease-free survival in lung cancer regardless of other factors, and reducing its levels through knockdown has been shown to lower the ability of tumors to grow.	NA	M – 213 FM - 253	65 (33 - 88)	Smoker and Non smoker	NA	The expression of KIF14 was markedly reduced in LUAD cells that were transfected with siRNA.	Li et al., 2023 [42]
Triple-Negative Breast Cancer	NA	KIF14 was found to be markedly upregulated in triple-negative breast cancer (TNBC), with its expression being associated with an unfavorable prognosis.	NA	NA	NA	NA	NA	Mutations in BRCA1 or BRCA2 are linked to genetic instability and significant chromosomal irregularities. It has been demonstrated that elevated levels of KIF14 expression are	Singel et al., 2014 [43]

								observed in non-cancerous, luminal breast tissue of individuals at high risk of BRCA mutation.	
Ovarian Cancer	NA	Therefore, understanding the mechanisms controlling the excessive production of KIF14 is essential in order to devise strategies for lowering KIF14 levels in OvCa cells as part of therapeutic interventions.	These potential transcriptional regulators could serve as potential targets for the development of specific anti-KIF14 therapy.	NA	NA	NA	NA	NA	Thériault et al., 2014 [44]

Figure 4. DNA base pair substitution and mutation:



Nucleotide grouping replacement or Compact discs change in various tissues. Nucleotide succession replacement or Disc transformation in various tissue types; (A) shows tissue-express sickness with DNA base pair substitution and most kinds of illness by and large having G > An and A > G substitution in KIF14 change. (B) DNA base pair substitution change in all tumors, and G > A 181; 21% and A > G 116; 13% were particularly changed. An, A, adenine; G, guanine; C, cytosine; T, thymine.

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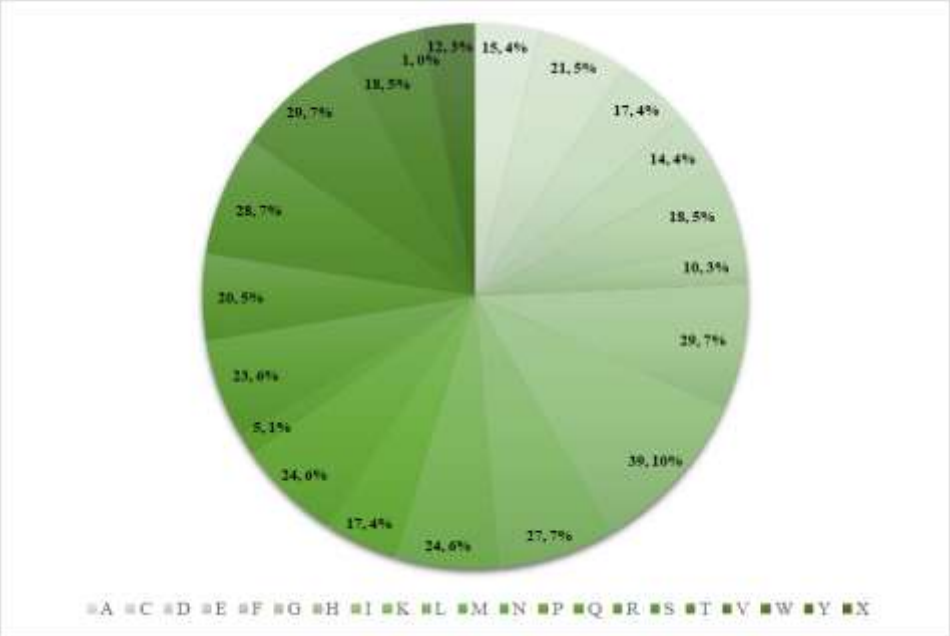
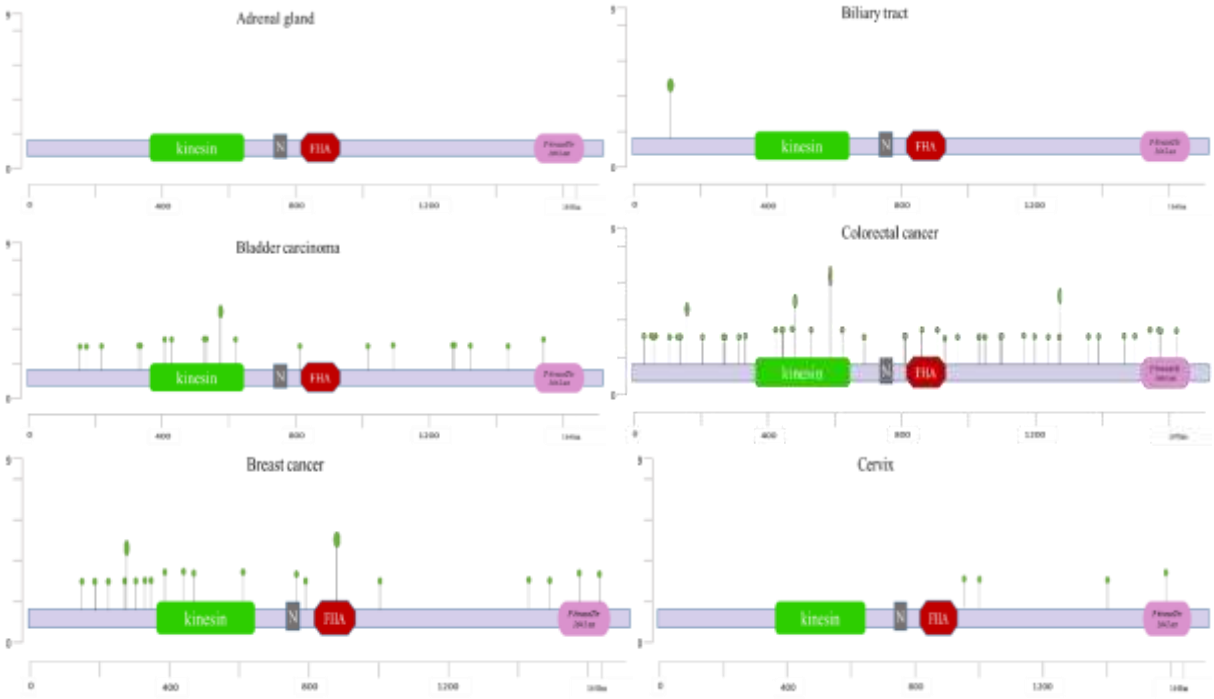
Figure 5. Amino acid changes in KIF14 mutation.



All cancer types' KIF14 AA alterations (by number and percentage) Labelling: AA, cases, %, etc. (A) AA alterations in various cancer types are particularly noticeable in the lung (Isoleucine 9) and endometrial (Isoleucine 11) cancers. (B) Analysis of amino acid (AA) modifications across all cancer types revealed that 10% of cases involved alterations in isoleucine, followed by histidine (7%), lysine (7%), serine (7%), and threonine (7%). Alterations in leucine, asparagine, and glutamine were each observed in 6% of cases, while changes in other amino acids occurred in 5% or fewer of cases. "X" represents a UTR or splice site

Figure 6 KIF14 mutation position in various cancers



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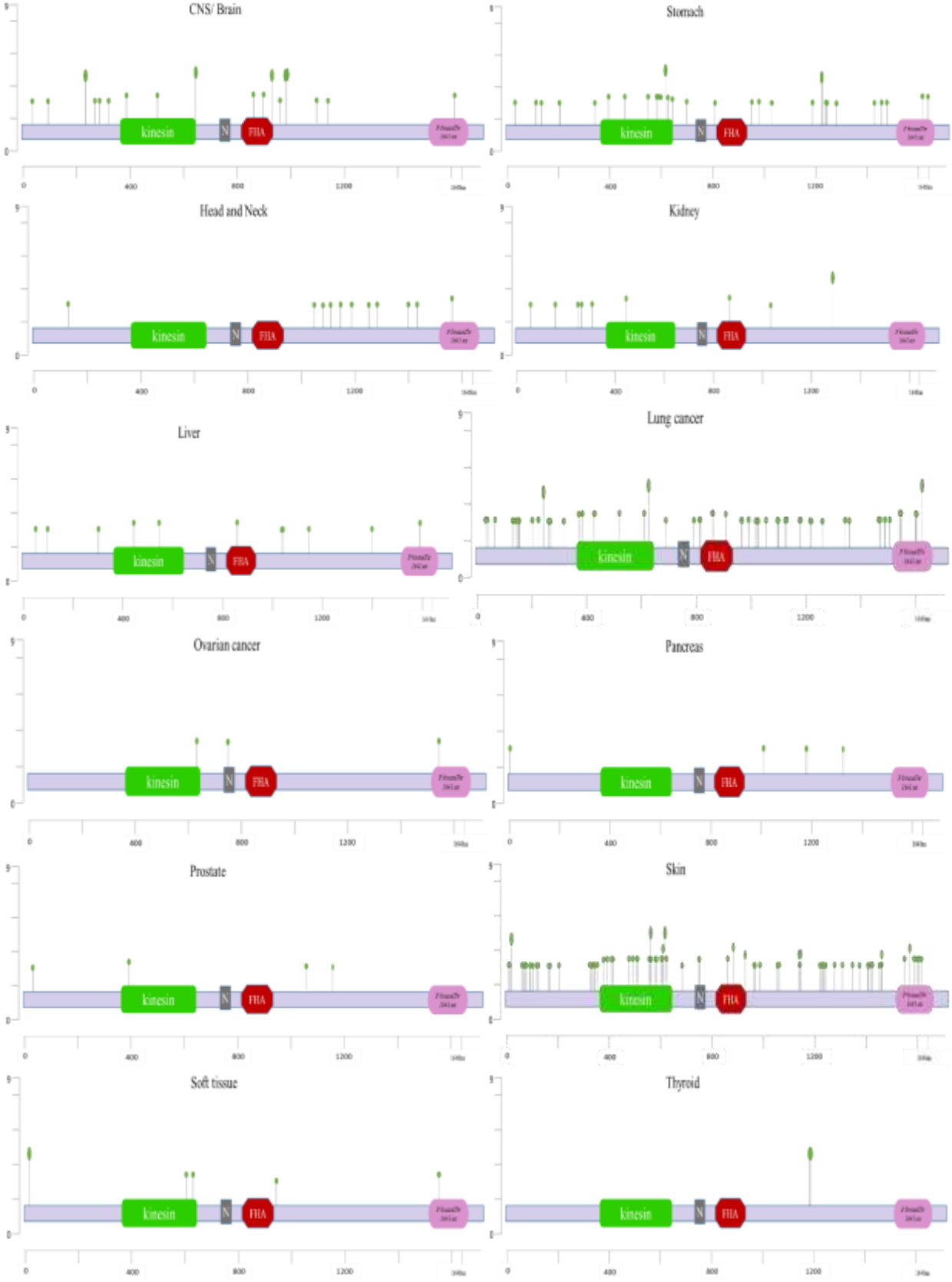

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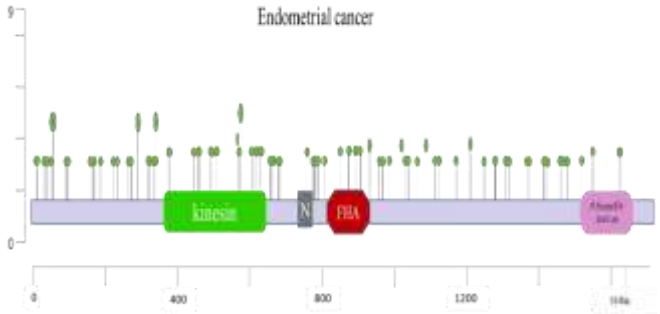

KIF14 mutations are analyzed to AA position. KIF14 protein AA mutation hotspots and the number of AA changed instances in various tissues. Endometrial cancer, cutaneous, and colorectal cancer are among cancers that have repetitive and severely changed AA changes. Overall, the findings indicate that KIF14 has mutations in all of its sections; as a result, all cancers have significant levels of mutations in the kinesin and FHA domains, which make them the primary hotspots for KIF14 mutation.

KIF14 and lung cancer promotion

Lung cancer is one of the predominant cancers worldwide. Early diagnosis, treatment, and prognosis can be improved by understanding the molecular mechanisms underlying lung cancer progression. Weighted gene co-expression network analysis was used to screen for core genes—those most strongly associated with lung cancer. To validate the effects of these core genes on lung cancer cell proliferation, matrix adhesion, and metabolic pathways, cell-based experiments were performed in vitro. Immunoglobulin superfamily member 10 (IGSF10) from the turquoise module, ribonucleotide reductase regulatory subunit M2, protein regulator of cytokinesis 1, and kinesin family members KIF14 and KIF2C from the brown module were identified as relevant, based on two gene modules and five core genes highly associated with lung cancer [26, 27]. Supervillin is a peripheral membrane protein involved in all stages of cell motility, including cell spreading. It is the largest member of the villin, gelsolin, and flightless family. Most known interactors bind at the amino (N)-terminus. Here, we demonstrate that the carboxyl (C)-terminus of supervillin can be modeled as gelsolin-like repeats and a villin-like headpiece connected by supervillin-specific loops. From yeast two-hybrid screens, 27 new potential interactors were identified. Twelve of these proteins (BUB1, EPLIN/LIMA1, FLNA, HAX1, KIF14, KIFC3, MIF4GD/SLIP1, ODF2/Cenexin, RHAMM, STARD9/KIF16A, Tks5/SH3PXD2A, TNFAIP1) co-localize with and mislocalize EGFP-supervillin in mammalian cells, suggesting in vivo association [8]. In breast cancer, accelerated cell proliferation is a coordinated process involving dysregulation of the cell cycle and activation of a specific gene expression program that determines tissue identity. Numerous studies have focused on molecules involved in cell proliferation and key regulatory transcription factors that control tissue-specific gene expression. BUB1, ANLN, KIF14, and NDC80 have been identified as potential breast cancer-associated genes [28]. The FHIT gene, which is frequently inactivated in lung cancer, acts as a tumor suppressor by promoting apoptosis and inhibiting proliferative growth; however, its exact mechanism is not fully understood. Transcriptional profiling demonstrated that the reintroduction of FHIT in lung cancer cells influenced DNA replication and chromosome segregation pathways. In particular, genes in the kinesin superfamily (KIFC1, KIF2C, KIF14, KIF11), centromeric proteins (CENPA, CENPF), and spindle-associated molecules (BUB1, BUB1B, AURKB, KNTC2) were downregulated. To determine whether loss of FHIT function in normal bronchial cells contributes to mitotic spindle defects, FHIT expression was silenced in human bronchial epithelial cells immortalized with hTERT and CDK4 (HBEC3KT) [29]. BUB1, TTK protein kinase, citron Rho-interacting kinase (CIT), ZAK, and NEK2 were upregulated in gastric cancer. Notably, BUB1, TTK, CIT, and NEK2 interacted with one another, functioned during multiple mitotic phases, and exhibited high expression levels. In addition, a subset of co-expressed genes—including KIF14, PRC1, CENPF, and CENPI—were functionally coupled with these kinases during mitosis. Validation assays confirmed that CIT, PRC1, TTK, and KIF14 were significantly upregulated in gastric cancer [30]. The kinesin superfamily of proteins (KIFs), also known as molecular motors, are microtubule-binding proteins involved in numerous biological processes, including cell division, intracellular transport, microtubule stabilization, and microtubule depolymerization. KIFs range from kinesin-1 to kinesin-14, comprising 45 members in 14 families, and perform a variety of biological functions in human tissues, particularly the brain [31]. For example, the KIF4A motor protein from the kinesin-4 family is essential for activity-dependent neuronal survival. Furthermore, there is a strong correlation between KIFC1/2C/4A/11/14/15/18A/18B/20B/23 and KRAS and TP53 mutation status [32]. These alterations have since been identified in multiple tumors at varying frequencies and confirmed through whole-genome sequencing. Such genetic modifications can alter the structural and functional properties of the KIF14 protein, leading to its overexpression and ligand-independent kinase activation. This results in persistent signaling and uncontrolled proliferation, contributing to oncogene addiction. Advances in genome and proteomic sequencing have provided the foundation to identify oncogenic mutations and amplifications. Our analysis provides comprehensive data

on KIF14 in normal cells and various cancers, enhancing research understanding and potentially aiding the discovery of novel therapeutic agents targeting these motor proteins and their associated signaling networks.

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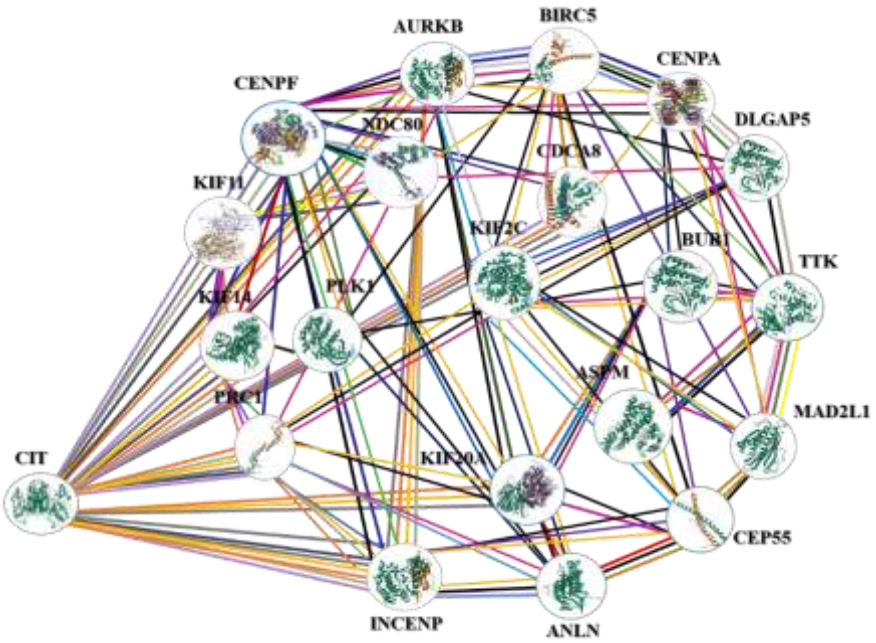

The KIF14 quality and furthermore interlinked significant protein network are associated with tumorigenesis.

Future perspectives

While studies have shown that KIF14 is essential for tumor cell proliferation in both in vitro and preclinical models, it has not yet been demonstrated clearly that KIF14 drives oncogenesis. We anticipate greater elucidation of KIF14's cellular roles in the coming years, as well as the discovery of other interacting partners and early therapeutic targeting of these interactions. But given the quick growth of ATPase inhibitors, we forecast that inhibitors of KIF14's enzymatic activity have been tested in clinical trials for a range of malignancies within a decade [33].

Future Directions for target confirmation:

As discussed throughout this text, kinesins have recently emerged as promising therapeutic targets in oncology, spurring substantial efforts toward the development of specific inhibitors. Although certain kinesin motor domains have been selectively investigated, it is important to recognize the challenges associated with targeting these domains, including concerns regarding specificity and toxicity [46]. A comprehensive structural analysis of the KIF14 protein, in conjunction with its known interactors—such as CIT, PRC1, supervillin, RIP2, and Radil—remains highly significant. Further insights are needed to elucidate the mechanisms by which KIF14 contributes to cytokinesis and oncogenic signaling, which may facilitate targeting cancer cell-specific interactions (rather than ATPase activity alone) to minimize off-target effects [47].

Additionally, investigating the transformative potential of KIF14 overexpression in various normal cell types will enhance the identification of tumorigenic pathways suitable for therapeutic intervention. It is also critical to validate KIF14 as a tumor biomarker, prognostic marker, and determinant of chemoresistance in larger, prospective patient cohorts. Such validation would enable KIF14 expression levels to serve not only as an early prognostic indicator but also as a bioindicator reflecting patient responses to targeted therapy—an essential component of personalized treatment strategies [48].

Conclusion:

We analysed the KIF14 oncogene's role in numerous disorders using human malignant growth genomic datasets. KIF14 quality articulation is related to different essential and metastatic disease movements. The late-stage distinguishing proof of KIF14 transformation, overexpression, and enhancement, exceptionally advances the growth movement. However lesser being developed. Generally speaking, the transformation and duplicate number variety of KIF14 from different malignant growth types explicitly lung, skin, and kidney are to a great extent modified by this quality. Our information demonstrates that the KIF14 is likely a sub-atomic marker and a suitable helpful objective for various sorts of malignant growth. Our analysis gives thorough data about KIF14 in different malignant growths which assists scientists with effective understanding for inhibition and to develop novel drugs.

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