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Research Article

KIF22 in the Prognosis and Immune Biomarking of Pan-Cancer

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KIF22, also known as kinesin-like DNA-binding protein (Kid), is a member of the Kinesin superfamily proteins (KIFs). Available evidence indicated that KIF22 was associated with cancer occurrence and development. However, the functions and underlying mechanisms of KIF22 in carcinogenesis and cancer progression remain largely unknown. In this study, we examined the expression profile and methylation status of KIF22 in different cancers, as well as its associations with prognosis, tumor stemness, genomic heterogeneity, immune evasion, immune infiltration, and therapeutic response in various tumor types. The results demonstrated that the expression level of KIF22 was higher in tumors than nontumor tissues and had strong relationships with prognosis, genomic heterogeneity, tumor stemness, neoantigen, ESTIMATE, and immune infiltration. KIF22 methylation status showed strong relationships with immunomodulators and chemokines. KIF22 had a significant relevance with drug susceptibility and could be a useful biomarker for forecasting survival probability and therapeutic reaction. Furthermore, KIF22 interaction and coexpression networks were mainly involved in cell division, cell cycle, DNA repair, and antigen processing and presentation. KIF22 could be used as a pan-cancer biomarker for clinical diagnosis, therapeutic schedule, prognosis, and cancer monitoring.

1. Introduction

Cancer is emerging as a major global health challenge. The number of cancer patients reached 19.3 million, and about 10 million died due to malignant tumors in 2020. The number of cancer and death cases will increase to more than 28 million and 16 million in 2040, respectively [1, 2]. Currently, chemotherapy, immunotherapy, radiotherapy, surgery, and targeted therapy are the mainstream treatment strategies [3]. These therapy strategies exhibit some clinical successes, but the survival ratio and prognosis of cancer patients remain unsatisfactory due to side effects, individual differences, drug resistance, and other reasons [4, 5]. For the above reasons, it is urgent to search for more effective therapeutic targets and novel sensitive cancer biomarkers for clinical diagnosis, therapeutic schedule, prognosis, and cancer monitoring.

Kinesin superfamily proteins (KIFs) are a class of highly conserved motor proteins that combine with microtubules and are involved in the transportation of various cargoes through microtubule-directed motility [6, 7]. KIFs are first discovered in squid tissue and are conserved in eukaryotes [8, 9]. Up to now, 45 KIF members have been identified in humans [9, 10]. On the basis of phylogenetic relationships, the KIFs are divided into 15 kinesin subfamilies, which are referred to as kinesin-1 to kinesin-14B. Based on the location of the motor domain in the molecules, these families can be approximately separated into three classes: N kinesins possess an amino-terminal motor domain, M kinesins possess a middle region motor domain, and C kinesins possess a carboxy-terminal motor domain [9, 11]. The physiological functions of these three families are different, N kinesins play roles in microtubule-plus-end-directed motility, C kinesins

play roles in microtubule-minus-end-directed motility, and M kinesins play roles in microtubule depolymerization [9, 11, 12]. At present, a large number of studies have revealed that the deviant expression level of KIFs may contribute to the progression of malignant neoplasms [13–16].

KIF22 has been reported to be a member of the kinesin-10 subfamily [17]. KIF22 is one of the N kinesins with an engine domain in the amino ending portion. KIF22 plays vital roles in microtubule-plus-end-directed motility and could bind directly to both chromosomes and microtubules [18]. It is well known that KIF22 mainly participates in regulating cytoskeletal dynamics, synaptic development, and microtubule stability [19, 20]. In prometaphase, KIF22 distributes along the chromosome and spindle structure [21]. During mitosis, it accumulates toward the metaphase plate and supplies a force to locate the chromosomes to the equator of the spindle [22]. When entering the anaphase, the KIF22 protein moves to the spindle poles together with chromosomes and promotes the compaction of chromosomes, which ensures the formation of normal nuclear and prevents the formation of multinucleated cells [23, 24]. The important roles of KIF22 in mitosis have been well studied, but the pan-cancer expression status, roles, and potential mechanisms of KIF22 in carcinogenesis and tumor progression remain to be studied.

In this study, we explored the expression of KIF22 in different tumors, nontumor tissues, and different human cell lines. Meanwhile, we investigated the biomarker relevance and prognostic value of KIF22 across different tumors. Furthermore, we also examined the relationships between KIF22 and immune infiltration, drug susceptibility, tumor stemness, genomic heterogeneity, and treatment response. To confirm the KIF22-related pathways, the interaction and coexpression networks of KIF22 were explored. This work would provide new insight into the role of KIF22 in cancer.

2. Materials and Methods

2.1. Gene Expression Analysis. The expression profile of KIF22 in human tumors and nontumor tissues were analyzed based on the TIMER database, the SangerBox website, and the GEPIA database. The HPA database and BioGPS database were utilized to investigate the expression profile of KIF22 in nontumor tissues and human cell lines [25–28]. The TISCH database was utilized to analyze the expression profile of KIF22 in diverse cell types from multiple cohorts [29, 30]. Besides, the protein level of KIF22 in human tumors was explored by immunohistochemical staining with HPA075670 antibody based on the HPA database. The cancer types analyzed in this study were listed in *Supplementary 1*.

2.2. Prognostic Analysis. The relevance between the expression level of KIF22 and the prognosis of patients with malignant tumors was analyzed based on Kaplan–Meier Plotter database, GEPIA database, SangerBox website, and PrognoScan database [31, 32].

2.3. Methylation Analysis. The methylation level of the KIF22 promoter in tumors and nontumor tissues was investigated based on the UALCAN database and DiseaseMeth database. The SurvivalMeth database was used to study the relationship between the methylation status of the KIF22 promoter and survival probability. The MethSurv database was utilized to study the association between methylation status of signal CpG island and survival rate [33–36]. The SangerBox website was utilized to investigate the relevance between the expression level of KIF22 and cancer stemness.

2.4. Genetic Alteration Analysis. The genetic alterations of KIF22 in various malignant neoplasms were investigated through the c-BioPortal database. The relationship between the expression level of KIF22 and genomic heterogeneity as well as the alteration landscape of KIF22 were explored based on the SangerBox website [37].

2.5. Interaction Network Analysis. The protein–protein interaction (PPI) network of KIF22 was analyzed via the STRING database. A total of fifty KIF22 binding proteins were used for KEGG and GO enrichment analysis through the SangerBox website. The gene–gene functional interaction network of KIF22 was analyzed via the GeneMANIA database [38, 39].

2.6. Molecular and Immune Subtype Analysis. The association between the expression level of KIF22 and immune or molecular subtypes in various malignant neoplasms was investigated by the TISIDB database [40].

2.7. Coexpression Network Analysis. The coexpression genes of KIF22 in HNSC were investigated by the LinkedOmics database [41]. Heat maps and volcano plots were used to display the coexpression genes. In addition, KEGG pathways and Gene Ontology biological processes of KIF22 and the coexpression genes were investigated and displayed via volcano plot and DAG.

2.8. Analysis of the Relationships between KIF22 and Immunomodulators, Neoantigen, Chemokines, and ESTIMATE. The relationships between the expression level of KIF22 and ESTIMATE and neoantigen were analyzed by the SangerBox website. The relevance between KIF22 and immunomodulators and chemokines was investigated via the TISIDB database.

2.9. Immune Cell Infiltration Analysis. The relationships between the expression level of KIF22 and the level of Th1 CD4+ T cell, follicular helper T cell, NK T cell, neutrophil, endothelial cell, CD8+ T Cell, regulatory T cell (Tregs), cancer-associated fibroblast, Th2 CD4+ T cell, and myeloid-derived suppressor cells (MDSCs) in the TME were analyzed by the TIMER database. Kaplan–Meier Plotter database was used for prognosis analysis based on KIF22 expression in relevant immune cell subgroups.

2.10. Drug Susceptibility and Therapy Response Analysis. The associations between drug susceptibility and the methylation, expression, and copy number variants (CNV) of KIF22 were analyzed by the RNAactDrug database [42]. The predictive power of KIF22 was analyzed via the TIDE server [43]. The

relevance between KIF22 expression and therapy response in breast cancer, glioblastoma multiforme, and ovarian cancer patients were investigated by the ROC plotter server [44].

3. Results

3.1. Expression Profile of KIF22 in Different Cancer Types. Compared with normal tissues, the expression level of KIF22 was markedly upregulated in most tumors including BRCA, BLCA, COAD, ESCA, HNSC, KIRP, KIRC, LIHC, LUSC, LUAD, PRAD, STAD, and UCEC (Figure 1(a)). Besides, the results analyzed, based on the GEPIA database, demonstrated that the expression level of KIF22 was apparently upregulated in most malignant neoplasms such as ACC, BRCA, BLCA, COAD, CESC, DLBC, GBM, HNSC, LGG, PCPG, PAAD, STAD, THYM, UCS, and UCEC (Figure 1(b)). The results from the SangerBox website were in keeping with the results from the TIMER and GEPIA databases (*Supplementary 2a*). In addition, immunohistochemical staining results of KIF22 demonstrated that the KIF22 protein level was higher in most tumors than noncancerous tissues (Figure 1(c)).

The expression level of KIF22 was low in most normal tissues but was high in lymph nodes, thymus, tonsils, and bone marrow (Figure 1(d)). In contrast, the KIF22 expression level was relatively high in most human cancer cell lines (Figure 1(e)). The results analyzed through the BioGPS database demonstrated that the KIF22 expression level was low in most normal tissues but was relatively high in CD71+ early erythroid (*Supplementary 2b*). Meanwhile, KIF22 expression level was upregulated in most human cancer cell lines (*Supplementary 2c*). Single-cell RNA sequencing data indicated that KIF22 expression level was associated with cell cycle progression (*Supplementary 2d*). These results demonstrated that KIF22 expression level was apparently upregulated in human tumors.

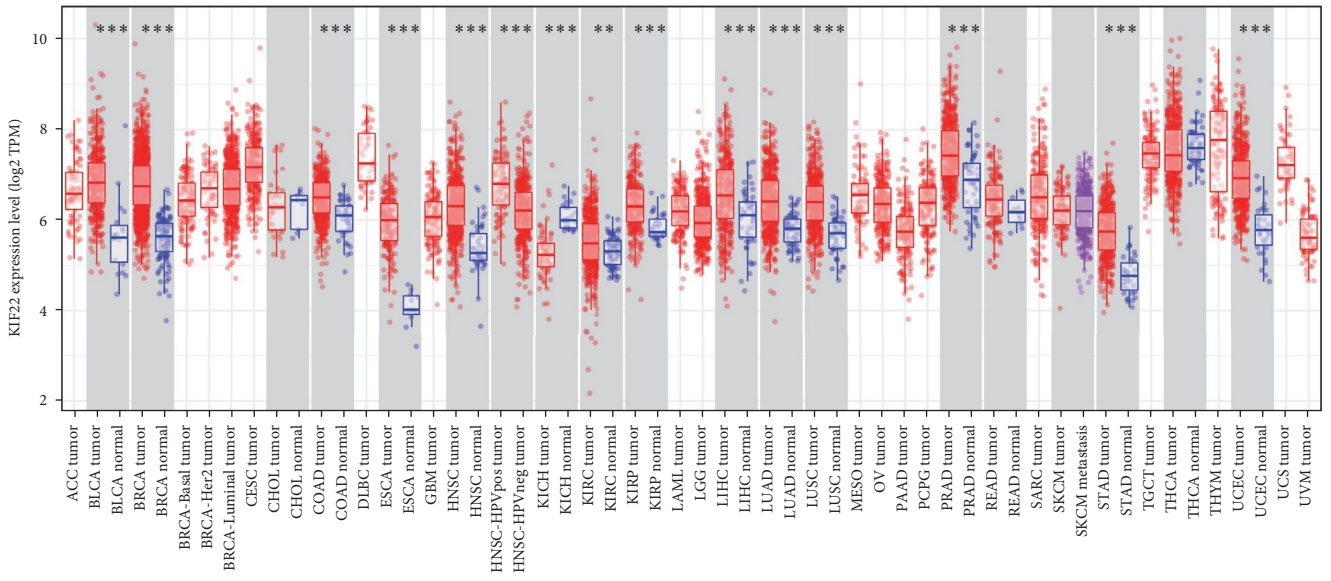
Furthermore, KIF22 exhibited cell-type-specific high expression in Tprolif cells from the THCA, SKCM, SCC, NSCLC, NPC, NHL, LIHC, KIRC, ESCA, CRC, CHOL, and BRCA cancer TME. In addition, KIF22 exhibited a wide range of expression in CD8+ T and mono/macro cells from various cancer TME (*Supplementary 3*). Details are displayed in *Supplementary 4*.

3.2. Prognostic Significance of KIF22. The prognostic significance of KIF22 in human cancers was investigated via Cox proportional hazards model and Kaplan–Meier survival curve. KIF22 expression was correlated negatively with overall survival in GBMLGG, ACC, LAML, KIRC, ALL-R, LGG, SKCM-M, UVM, SKCM and positively with overall survival in CESC, OV, and THYM (Figure 2(a)), negatively with disease-free interval in SARC, KIRP, KIPAN and positively with disease-free interval in PCPG (Figure 2(b)), negatively with disease-specific survival in ACC, GBMLGG, KIRC, SKCM-M, KIPAN, UVM, LGG, SKCM and positively with disease-specific survival in OV and CESC (Figure 2(c)), negatively with progression-free interval in ACC, UVM, KIRP, UCS and positively with progression-free interval in PCPG (Figure 2(d)).

The Kaplan–Meier survival curve indicated that higher level of KIF22 indicated a worse overall survival rate in ESAD, KIRC, LIHC, SARC, UCEC, better overall survival rate in CESC, HNSC, STAD, THYM, THCA, worse RFS in ESAD, KIRC, LIHC, LUSC, SARC, UCEC, and better RFS in HNSC and PCPG (Figure 2(e)). The results analyzed based on the GEPIA database revealed that a higher level of KIF22 was closely related to worse overall survival rate in ACC, KIRC, PRAD, SKCM, UVM, better overall survival rate in CESC, OV, THYM, poorer DFS in ACC, PRAD, SARC, and UVM (*Supplementary 5*). Additionally, the PrognoScan database was used to examine the relevance between KIF22 expression and prognoses of cancer patients. Poorer prognosis was associated with higher KIF22 expression in the bladder, brain, eye, prostate, skin, and soft tissue malignancies (*Supplementary 6*). The results presented above demonstrated a close association between KIF22 expression and prognoses.

3.3. KIF22 Correlates with Cancer Stemness. Previous studies have reported that the gain of stem-cell-like and progenitor characteristics and gradual loss of the differentiation characteristics were common events along the progression of cancer [45]. The expression level of KIF22 was positively related to cancer stemness in most malignant neoplasms but was negatively associated with cancer stemness in THYM, KIPAN, PRAD, THCA, and ACC (Figure 3(a)). The dysregulation of epigenetic modification in cancer cells often leads to stemness feature acquisition and oncogenic dedifferentiation [46, 47]. KIF22 promoter was hypomethylated in COAD, LIHC, BLCA, PRAD, TGCT, UCEC, THCA, and hypermethylated in BRCA, CESC, CHOL, ESCA, HNSC, KIRC, LUSC, and SKCM compared with nontumor tissues (Figure 3(b)). Besides, survival probability was closely related to the methylation level of KIF22 promoter (Figure 3(c)). The results analyzed based on the MethSurv database showed a close correlation between prognosis and the methylation level of a single CpG island in the KIF22 promoter (Figure 3(d)). Detailed information is displayed in *Supplementary 7*. These results indicated a strong association between cancer stemness and KIF22 expression. The methylation status of KIF22 promoter was closely related to the prognosis of cancer patients.

3.4. KIF22 Correlates with Genomic Heterogeneity. Heterogeneity frequently leads to drug resistance to cancer and results in poor prognosis [48]. The expression level of KIF22 was correlated positively with genomic heterogeneity in most tumor types except THYM (Figure 4(a)). Tumor patients with different mutation profiles may give out different responses to therapy [48]. About 1.8% of cancer patients showed genetic alteration in KIF22. The most common genetic alteration types were amplification, missense mutation, and truncating mutation (Figure 4(b)). The mutation occurred at different sites of KIF22, including the KISc KID-like and HHH 3 domains. The mutation frequency of KIF22 ranged from 0.2% to 4.0% in different cancer types, with 4.0% in UCEC being the highest and 0.2% in LGG being the lowest, respectively (Figure 4(c)). Additionally, the results analyzed based



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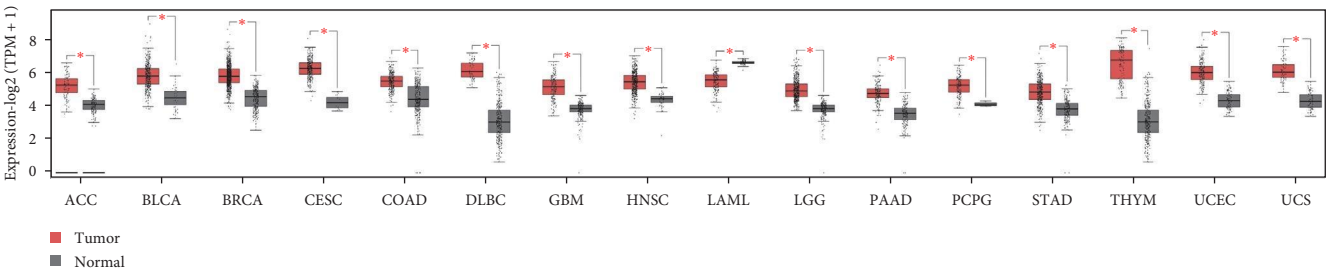

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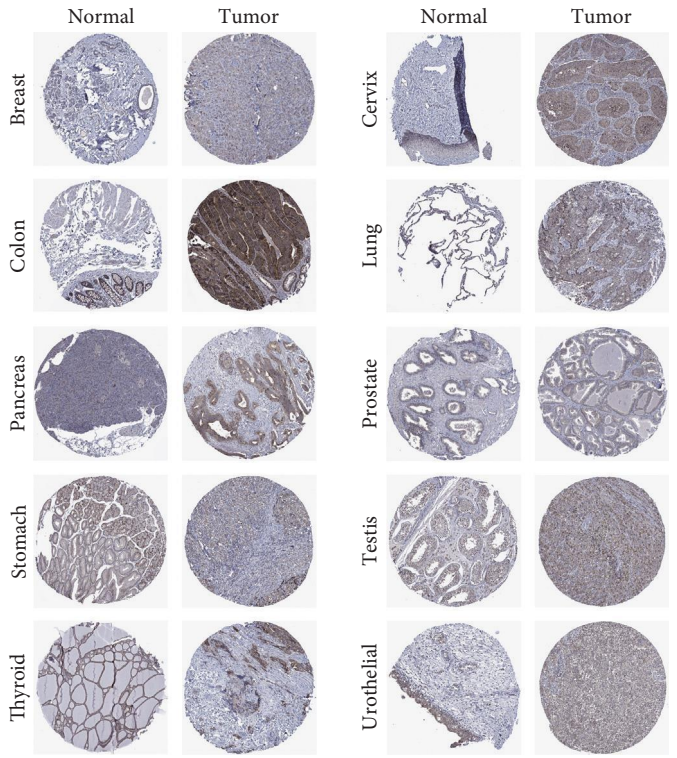

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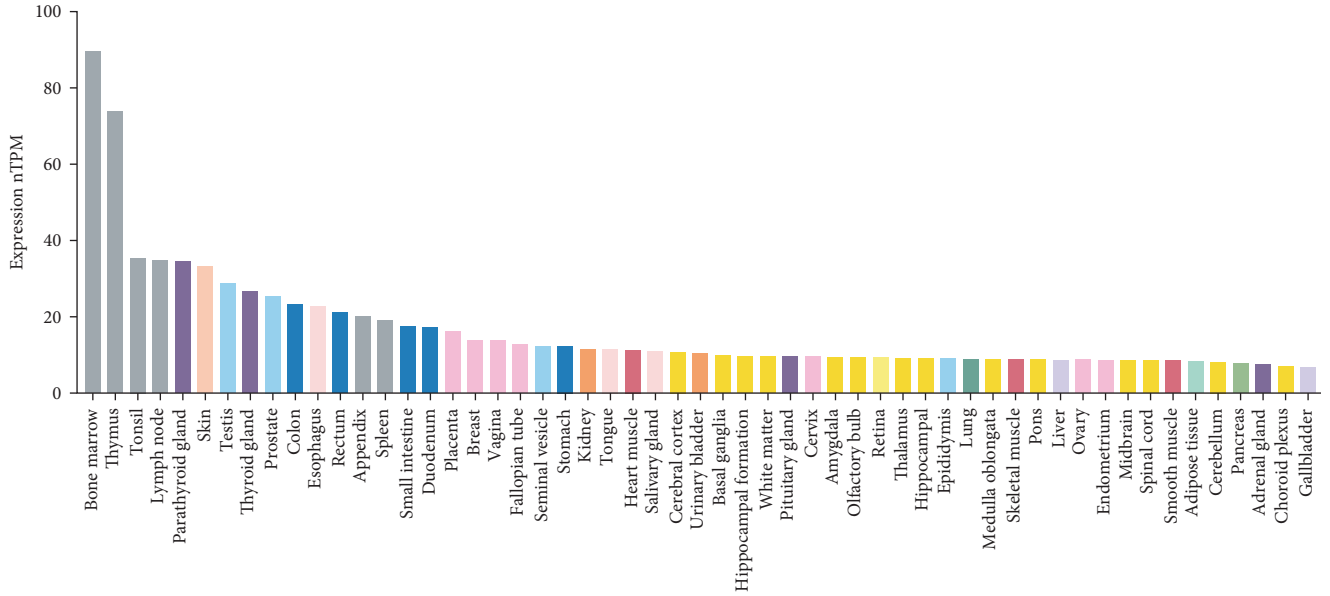

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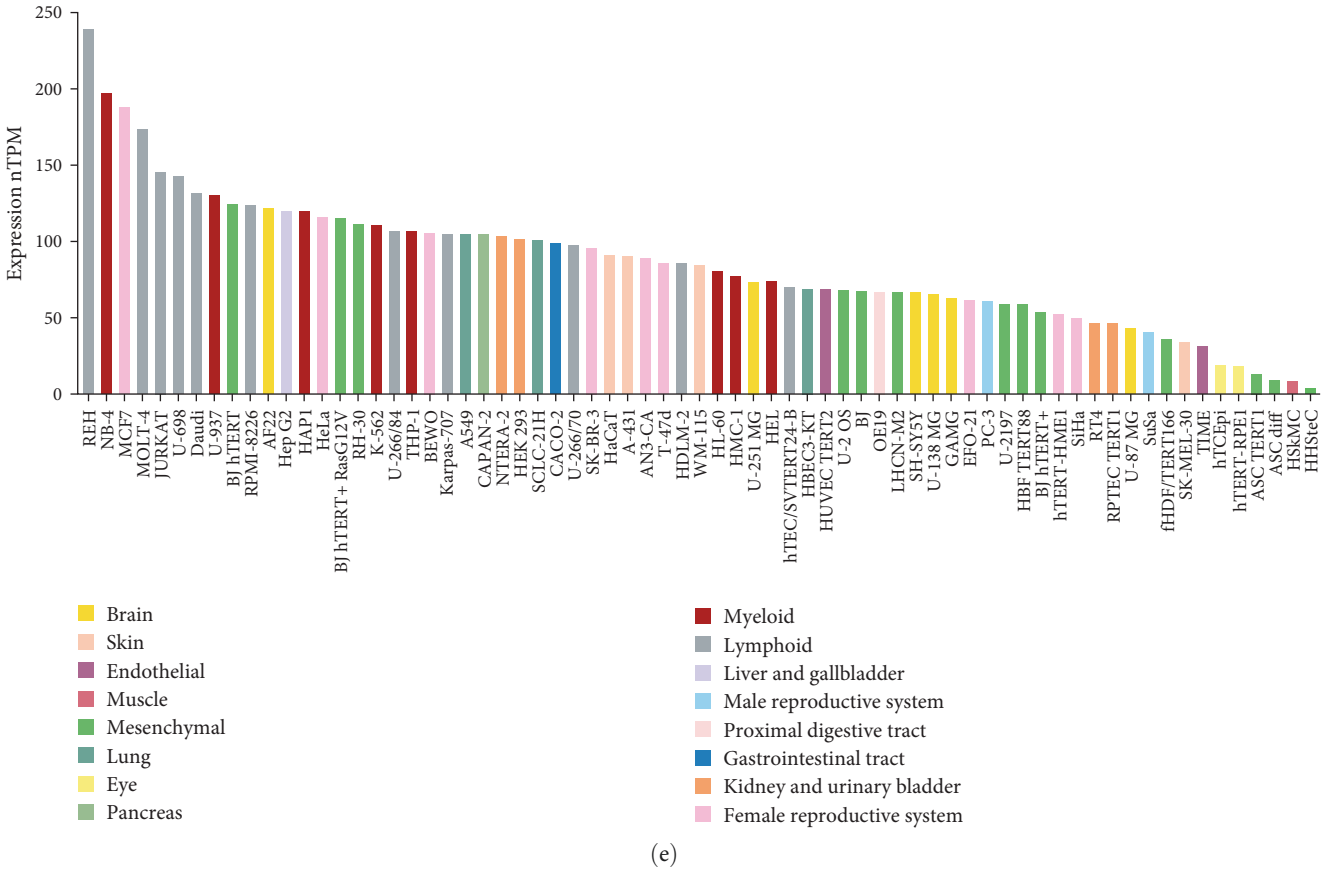

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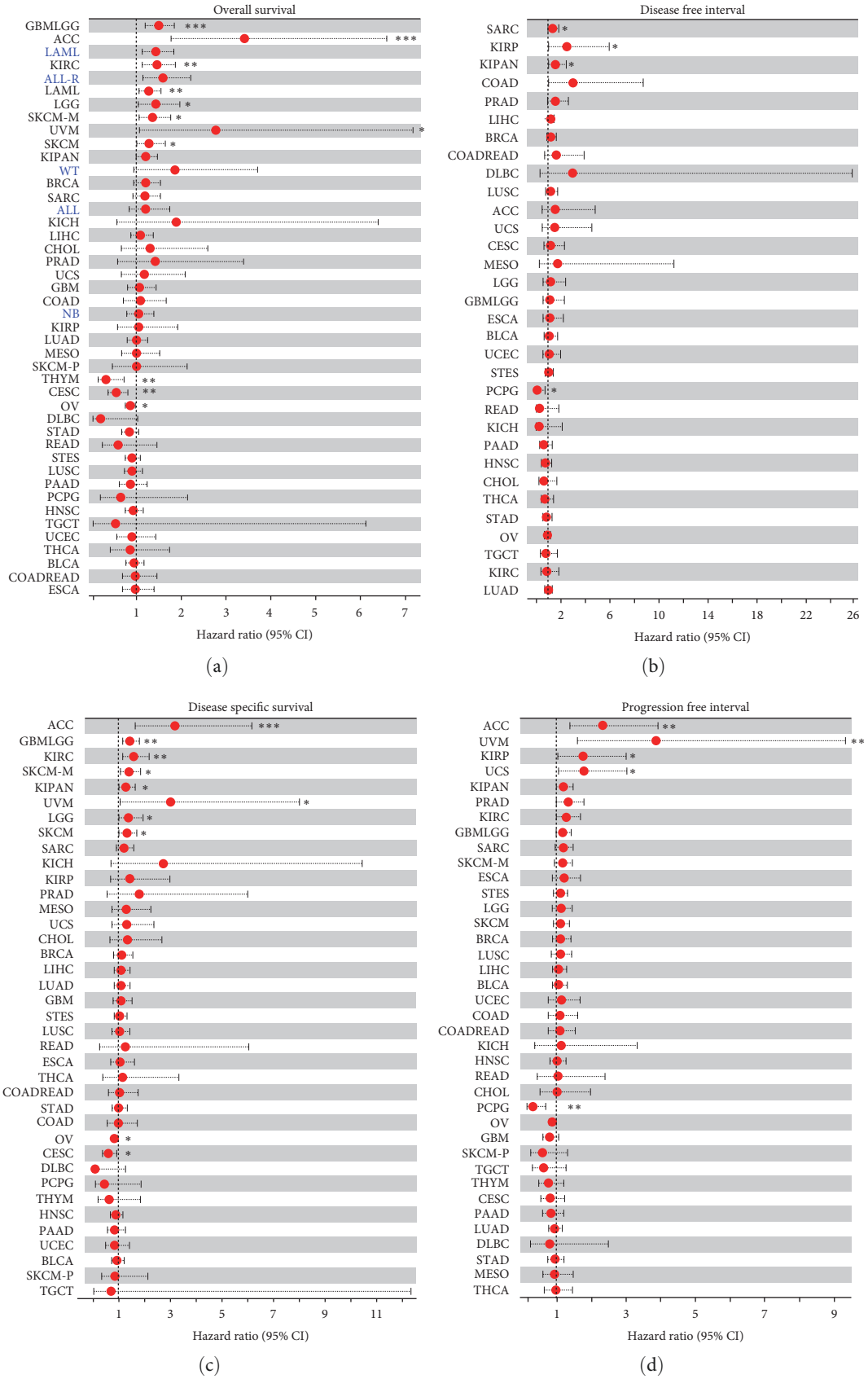
Figure 1: The expression level of KIF22 in different tumors. (a) KIF22 expression profile in different tumors and noncancerous tissues based on TIMER. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. (b) KIF22 expression profile in different tumors and noncancerous tissues based on GEPIA. (c) Representative immunohistochemistry images of KIF22 in breast, cervix, colon, lung, pancreas, prostate, stomach, testis, thyroid, urothelial cancer tissues, and noncancerous tissues analyzed through HPA database. (d) KIF22 mRNA expression profile in human normal tissues based on HPA. (e) KIF22 mRNA expression level in different cell lines based on HPA.



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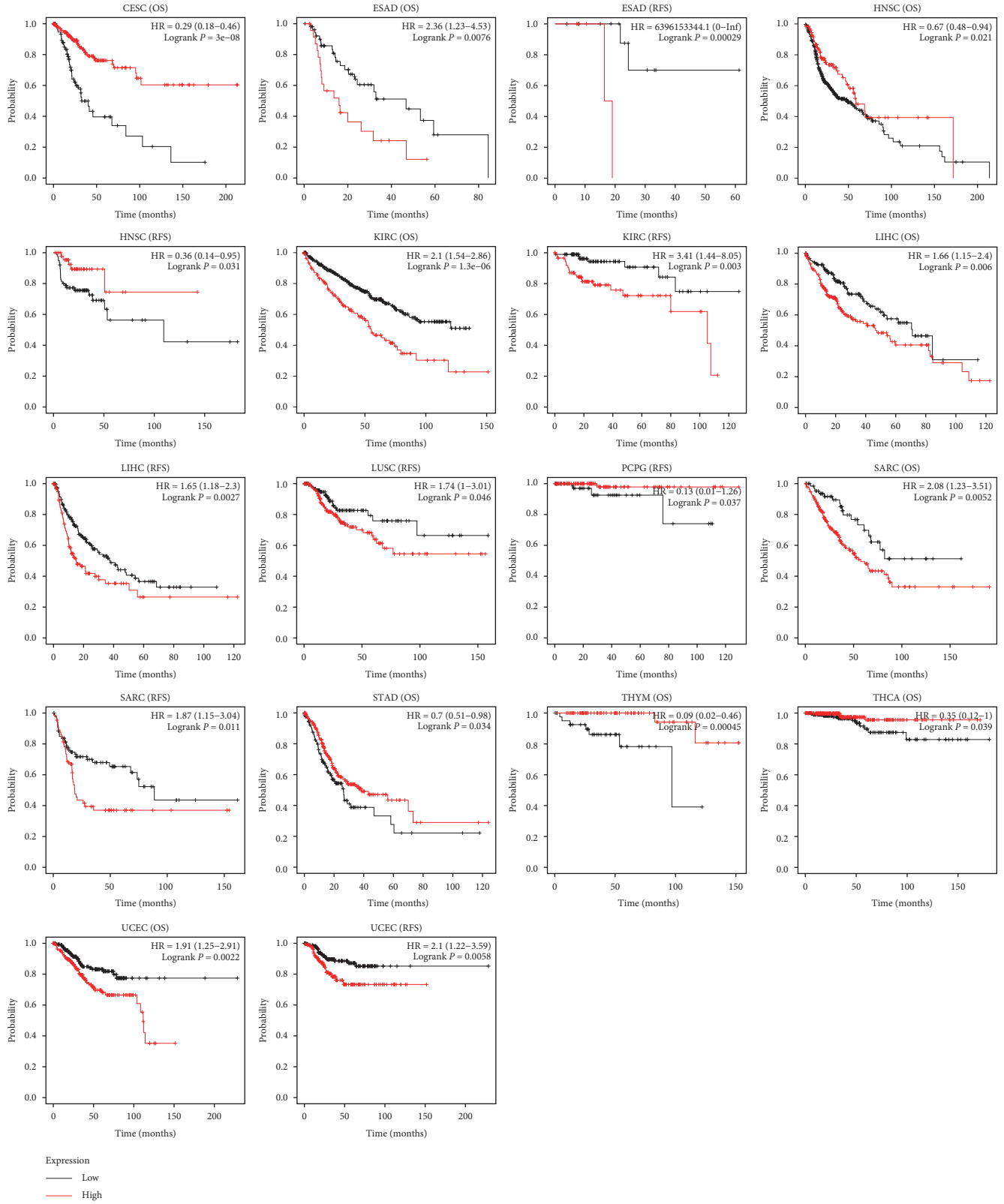

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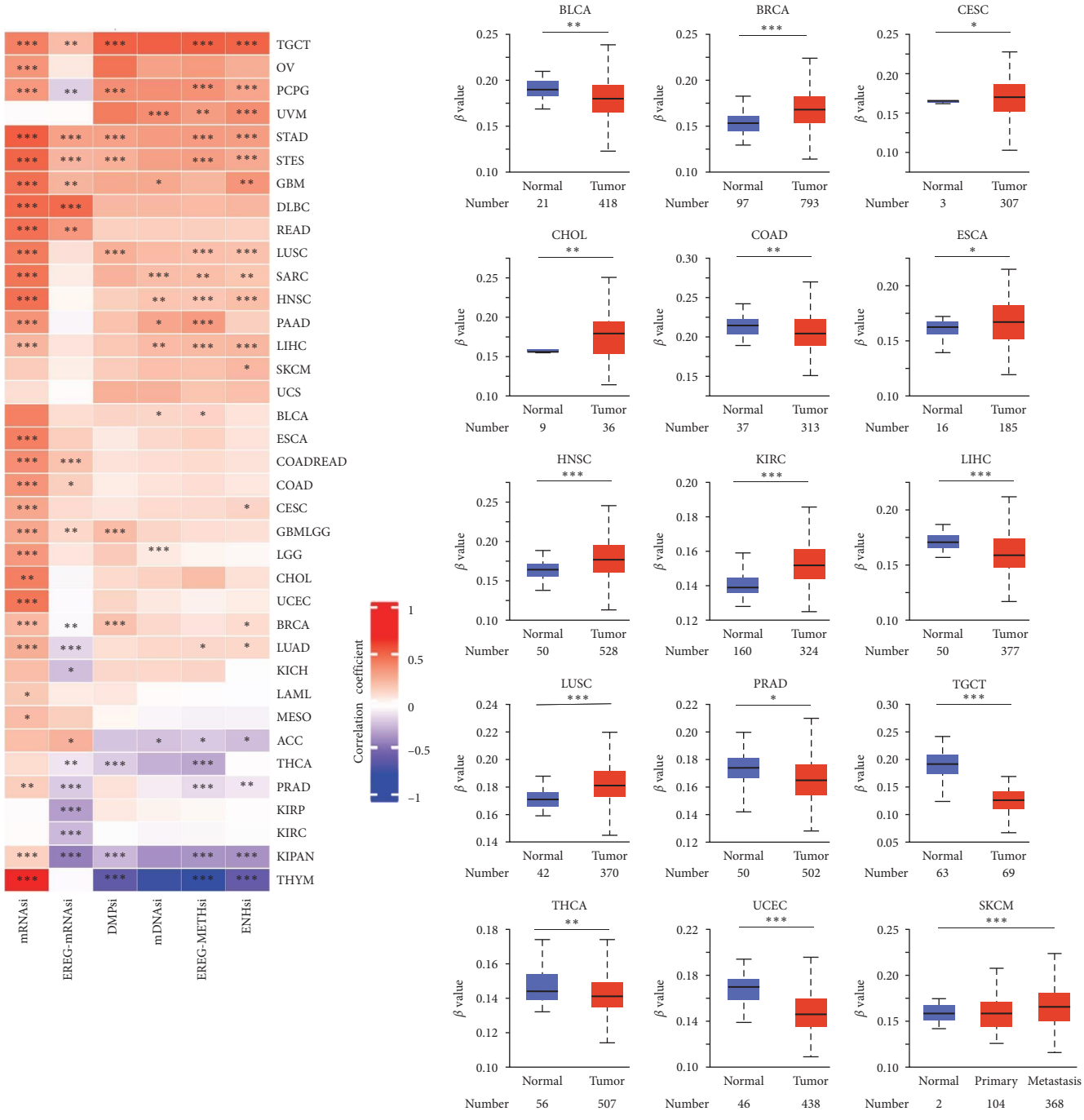
Figure 2: The prognostic significance of KIF22 in human tumors. (a) Univariate Cox regression of KIF22 expression level for overall survival. Blue word: data from TARGET, others: data from TCGA. (b) Univariate Cox regression of KIF22 expression level for disease free interval. (c) Univariate Cox regression of KIF22 expression level for disease specific survival. (d) Univariate Cox regression of KIF22 expression level for progression free interval. (e) Survival probability of different cancer patients with high and low KIF22 expression based on Kaplan–Meier survival curve analysis.



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on the cBioPortal database demonstrated that UCEC had the highest mutation frequency in KIF22, LGG had a lower mutation frequency in KIF22, and THCA, CHOL, TGCT, PCPG, UVM, THYM, KIRP, KICH, and ACC had on mutation in KIF22 (Figure 4(d)). Changes in gene expression were caused by various types of KIF22 alterations (Figure 4(e)). Cancer patients with genetic changes in KIF22 had better progression-free survival rates, disease-specific survival rates, and overall survival rates than patients without mutations (Figure 4(f)). Altogether, these findings suggested a strong correlation between genomic heterogeneity and KIF22 expression. Many human malignancies had KIF22 genetic mutations, which might be crucial to the development of tumors.

3.5. Enrichment Analysis of KIF22-Related Partners. The gene–gene functional interaction network showed that KIF22 and the related genes were mainly correlated with the microtubule-associated complex and antigen processing

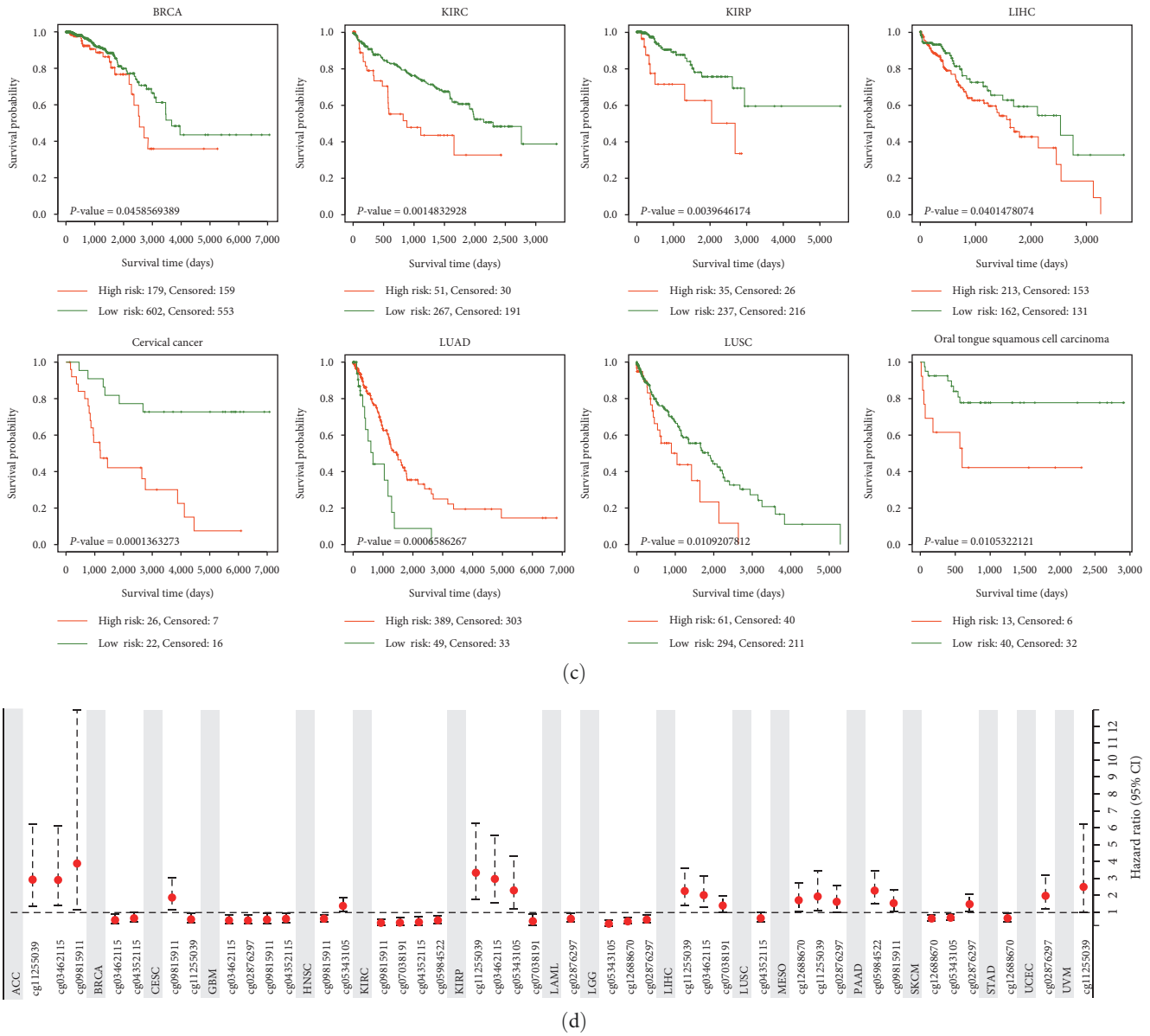
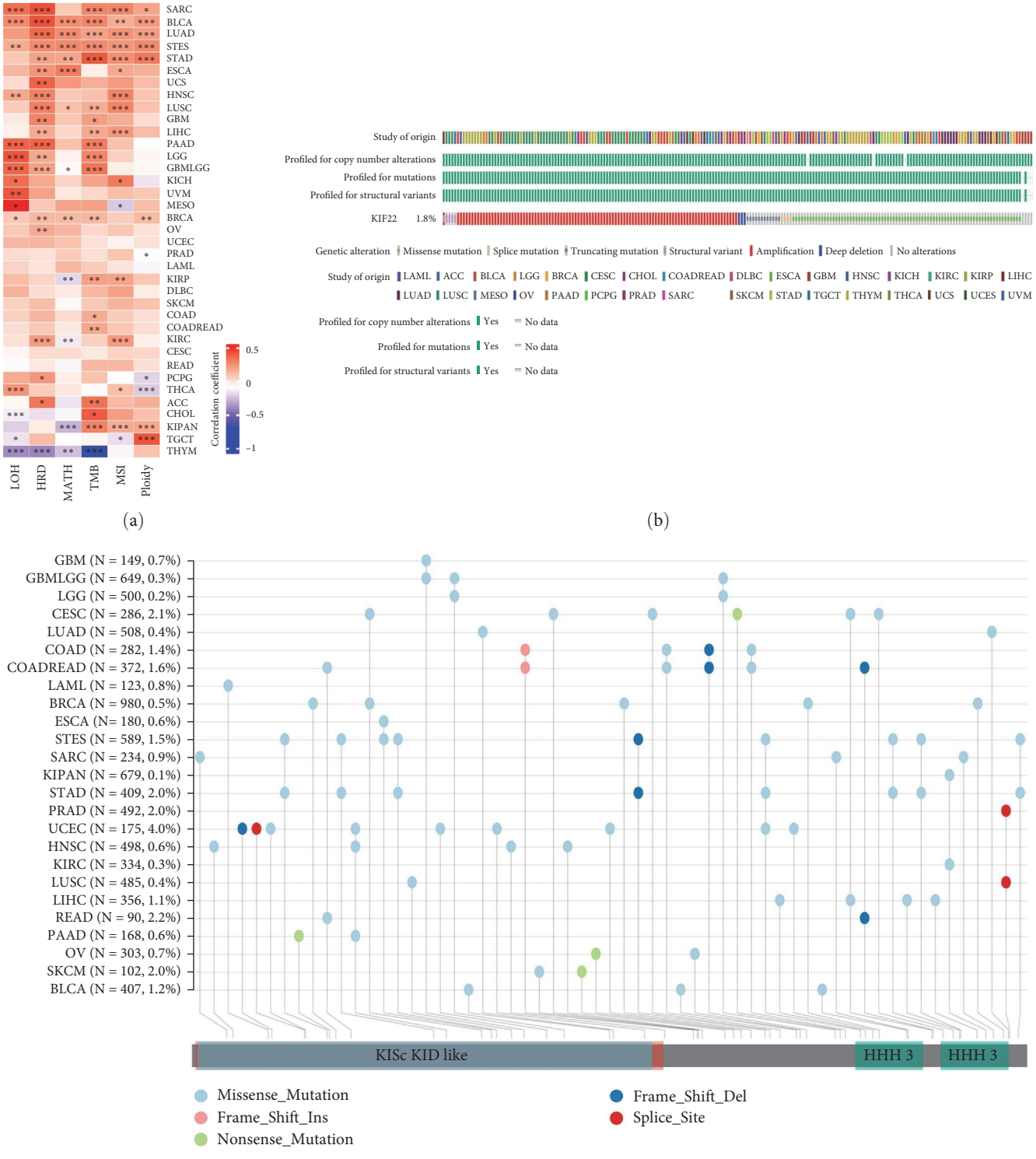


FIGURE 3: The association between KIF22 and cancer stemness, and methylation modification of KIF22 in different tumors. (a) The relationship between KIF22 expression level and EREG-mRNAsi, DMPsi, EREG-METHsi, mDNAsi, mRNAsi, ENHsi. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. (b) The methylation level of KIF22 promoter in tumors and noncancerous tissues based on TCGA. (c) The association between KIF22 methylation status and survival probability based on SurvivalMeth. (d) Univariate Cox regression of the single CpG island methylation status in KIF22 promoter for prognosis of cancer patients based on MethSurv.

and presentation (Figure 5(a)). To further study the molecular function of KIF22, the PPI network was explored through STRING database (Figure 5(b)). Fifty KIF22 interacting proteins were selected for further KEGG and GO analysis. The result indicated that KIF22 presented in different cellular components, including cell division site, cleavage furrow, microtubule end, and kinesin complex (Figure 5(c)). Microtubule plus-end binding, ATP-dependent microtubule motor activity, microtubule motor activity, tubulin binding, and kinesin binding were the main molecular functions of KIF22 (Figure 5(d)). The KEGG pathway enrichment analysis showed that KIF22 was mainly correlated with Huntington's disease, salmonella infection, endocytosis, and vasopressin-regulated water reabsorption (Figure 5(e)). KIF22 was mainly involved in mitotic spindle organization, nuclear chromosome segregation, sister chromatid segregation, retrograde vesicle-mediated transport, nuclear division, and antigen processing and presentation (Figure 5(f)). These results suggested that KIF22 might be crucial for immune response and cell division.

3.6. KIF22 Correlates with Immune and Molecular Subtypes. KIF22 is expressed at a different level in different molecular or immune subtypes. For molecular subtypes, KIF22 showed the highest expression level in primitive molecular subtype



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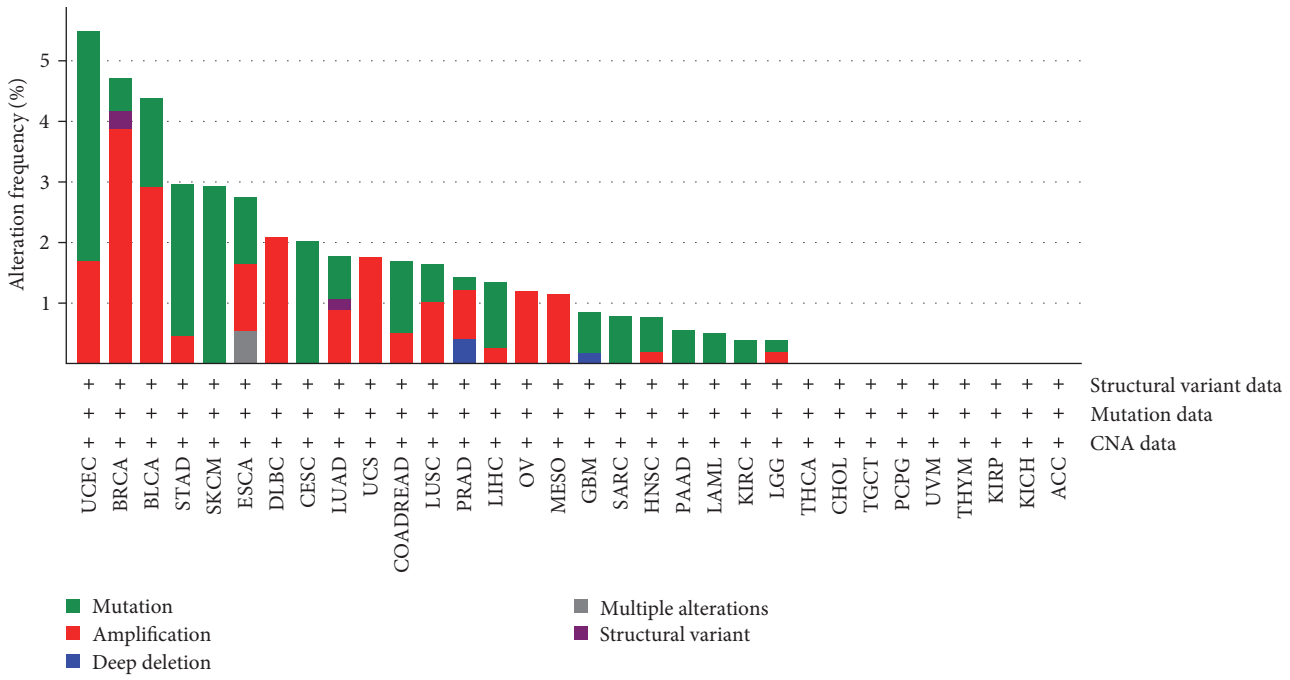

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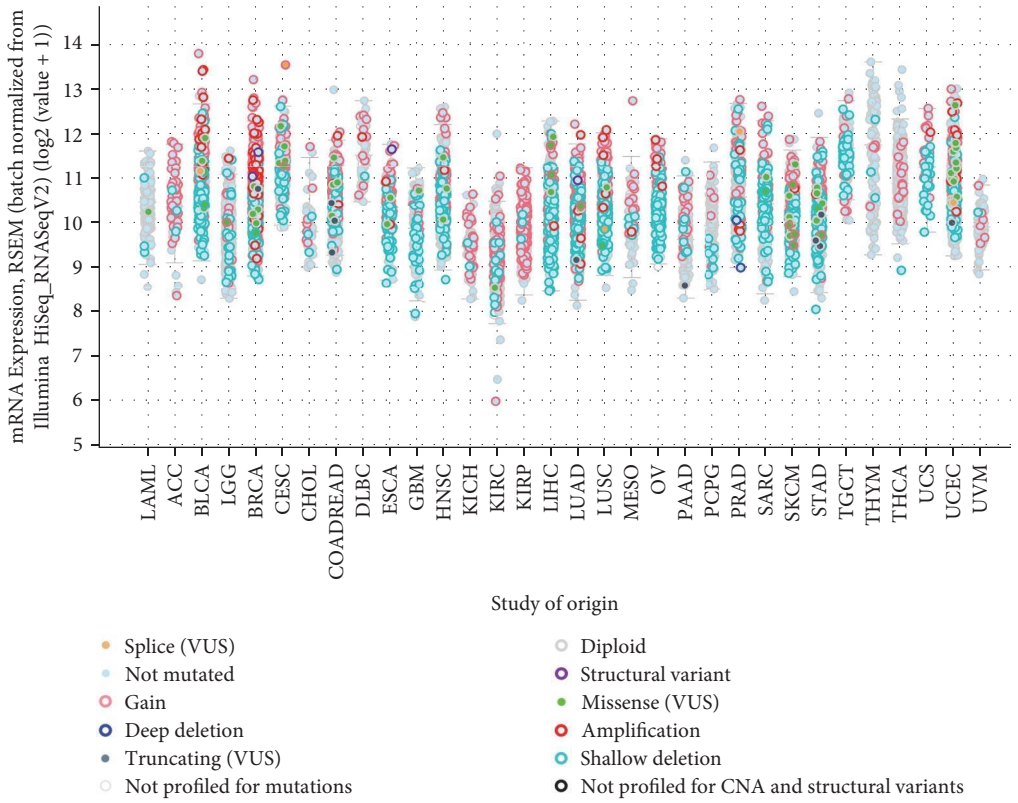

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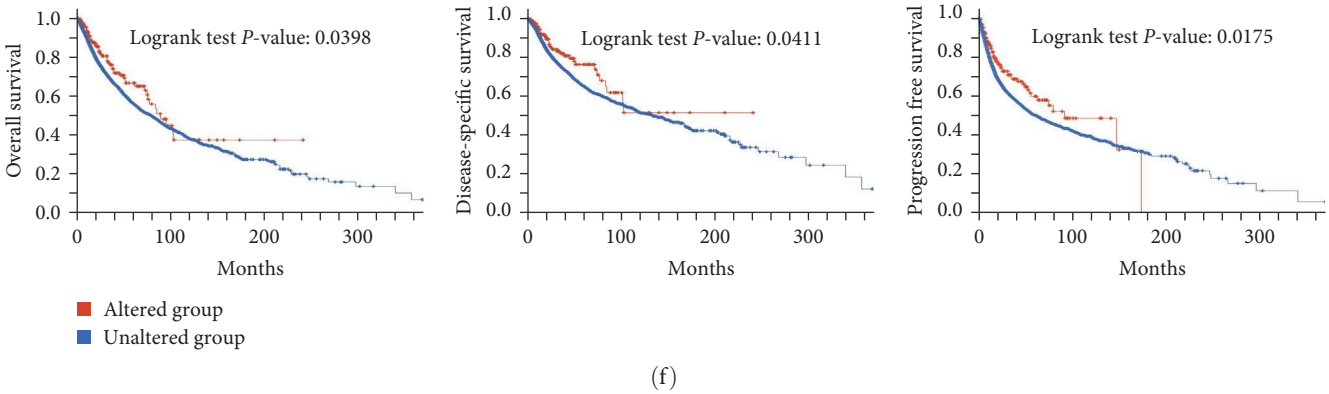


(f)

Figure 4: The association between KIF22 and tumor heterogeneity, and genetic alteration of KIF22 in different tumors. (a) The relationship between KIF22 expression level and ploidy, LOH, HRD, MSI, TMB, MATH. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. (b) Alteration landscape of KIF22 in different tumors. (c) KIF22 mutation points in different tumors. (d) KIF22 alteration frequency in different tumors. (e) The expression level of KIF22 in different tumors with various alteration types. (f) The Kaplan–Meier curves of OS, DSS, PFS in KIF22 altered group and KIF22 unaltered group.

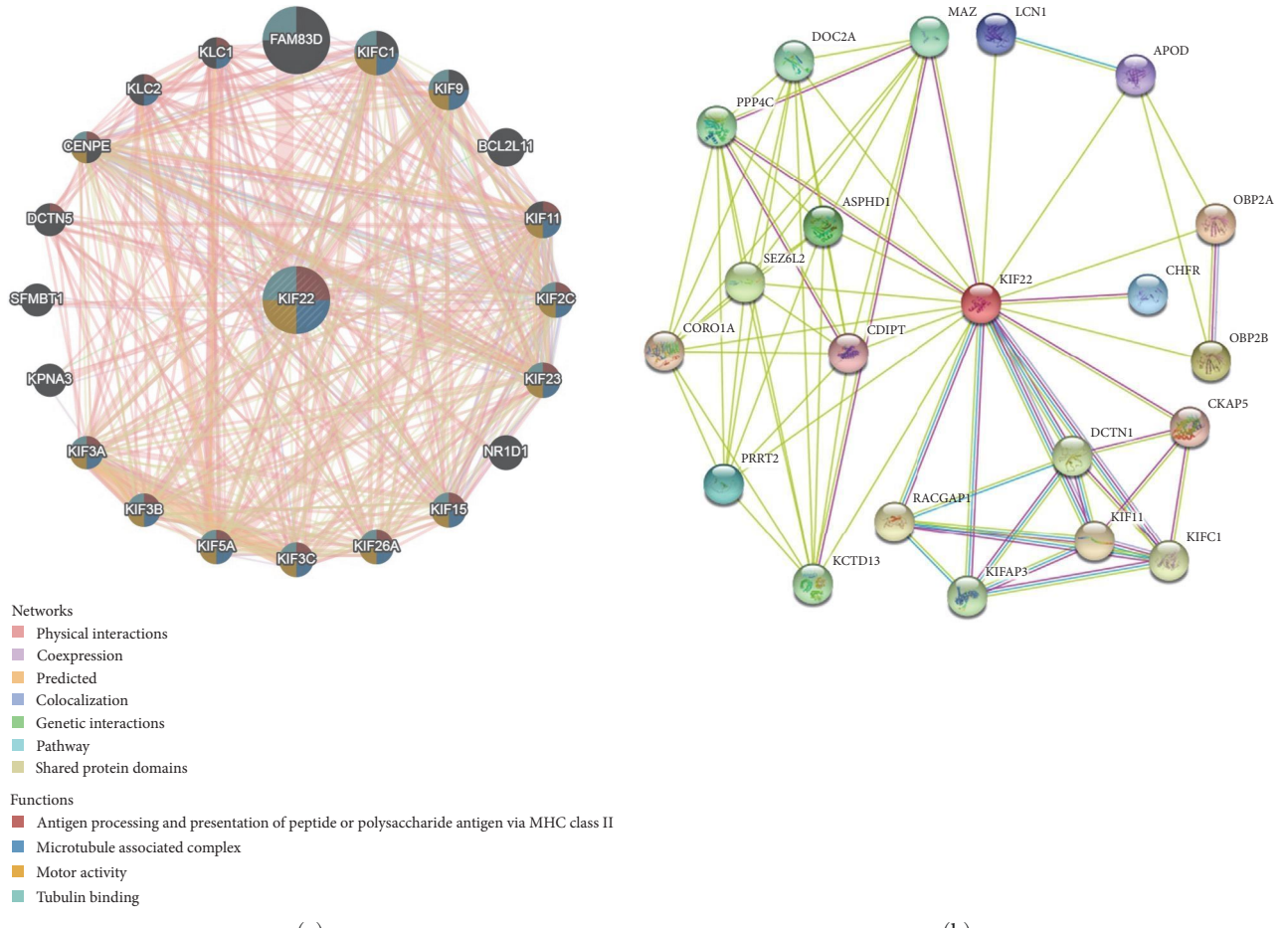
of LUSC, CIMP-intermediate molecular subtype of ACC, G-CIMP-low molecular subtype of GBM and LGG, 7-IDH1 molecular subtype of PRAD, iCluster:3 molecular subtype of LIHC, atypical molecular subtype of HNSC, C2b molecular subtype of KIRP, GS molecular subtype of READ, ESCC molecular subtype of ESCA, HM-indel molecular subtype of STAD, HM-SNV molecular subtype of COAD, immunoreactive molecular subtype of OV, kinase signaling molecular subtype of PCPG, and LumB molecular subtype of BRCA (Figure 6).

For immune subtypes, KIF22 showed the highest expression level in C1 (wound healing) immune subtype of LUAD, UCS, READ, KIRC, KIRP, BRCA, and KICH, C2 (IFNγ dominant) immune subtype of PAAD, UCEC, CHOL, SARC, and TGCT, C3 (inflammatory) immune subtype of SKCM, C4 (lymphocyte depleted) immune subtype of ACC, PRAD, and LGG, and C5 (immunologically quiet) immune subtype of PCPG (Figure 7 and *Supplementary 8*). Above results demonstrated that KIF22 expression were various in different immune and molecular subtypes.

3.7. KIF22 Correlates with Neoantigen, Immunomodulators, Chemokines, and ESTIMATE. Immunomodulators, including immunostimulators, immunoinhibitors, and MHC molecules, play critical roles in immunotherapy and tumor immune infiltration by regulating the immune inhibitory and stimulatory pathways [49]. KIF22 methylation status was correlated positively with most immunostimulators in PRAD, UCEC, LUAD, BLCA, STAD, PAAD, KIRP, LUSC, CESC, KICH, LIHC, THCA, and BRCA, but negatively with most immunostimulators in OV and TGCT (Figure 8(a)). In addition, KIF22 methylation status was correlated positively with most immunoinhibitors in UCEC, BRCA, STAD, LUAD, CESC, LIHC, PRAD, KICH, LUSC, KIRP, PAAD, THCA, and BLCA, but negatively with most immunoinhibitors in OV and TGCT (Figure 8(b)). Furthermore, KIF22 methylation status was correlated positively with most MHC molecules in KIRP, UVM, BRCA, KICH, THCA, CESC, LUSC, PAAD, LUAD, STAD, PRAD, UCEC, and BLCA, but negatively with most MHC molecules in HNSC and TGCT (Figure 8(c)). Chemokines play important roles in host defense by controlling cell migration during inflammation and immune surveillance [50]. KIF22 methylation status was correlated positively with most chemokines in STAD, BLCA, THCA, BRCA, KIRP, LIHC, PRAD, LUAD, PAAD, LUSC, KICH, and UCEC (Figure 8(d)). In addition, KIF22 methylation status was correlated positively with most chemokine receptors in LUSC, LIHC, KIRP, BLCA, BRCA, KICH, STAD, PAAD, THCA, LUAD, and PRAD, but negatively with most chemokine receptors in TGCT (Figure 8(e)). These results indicated that KIF22 might play important roles in coordinating the role of these immunomodulators and chemokines in different pathways and could be selected as a pan-cancer immunotherapy biomarker for treatment-response prediction.

A group of abnormal proteins that are encoded by mutant genes in tumors are known as tumor neoantigens. The tumor neoantigens are important for T cell-mediated antitumor immune response as well as tumor immunotherapy [51]. In LUAD, LGG, BRCA, STAD, HNSC, and LUSC, the expression of KIF22 was positively related to neoantigens (Figure 8(f)). The relevance between KIF22 expression and ESTIMATE was examined to further understand the functions of KIF22 in the immunological response. The results showed that the expression level of KIF22 was negatively related to ESTIMATE in most human tumors, but correlated positively with ESTIMATE in UVM, THYM, and TGCT (Figure 8(g)). Overall, these results demonstrated that KIF22 might have important functions in antitumor immunity by controlling the immune mechanism as well as the composition in TME.

3.8. KIF22 Correlates with Tumor Immune Infiltration. The above results demonstrated that KIF22 expression level was diverse in different immune subtypes and was closely correlated with immunomodulators, chemokines, neoantigen, and ESTIMATE. Next, we explored the association between KIF22 expression level and immune cell infiltration based on the TIMER database. The results indicated that KIF22 expression showed a positive relationship with the infiltration



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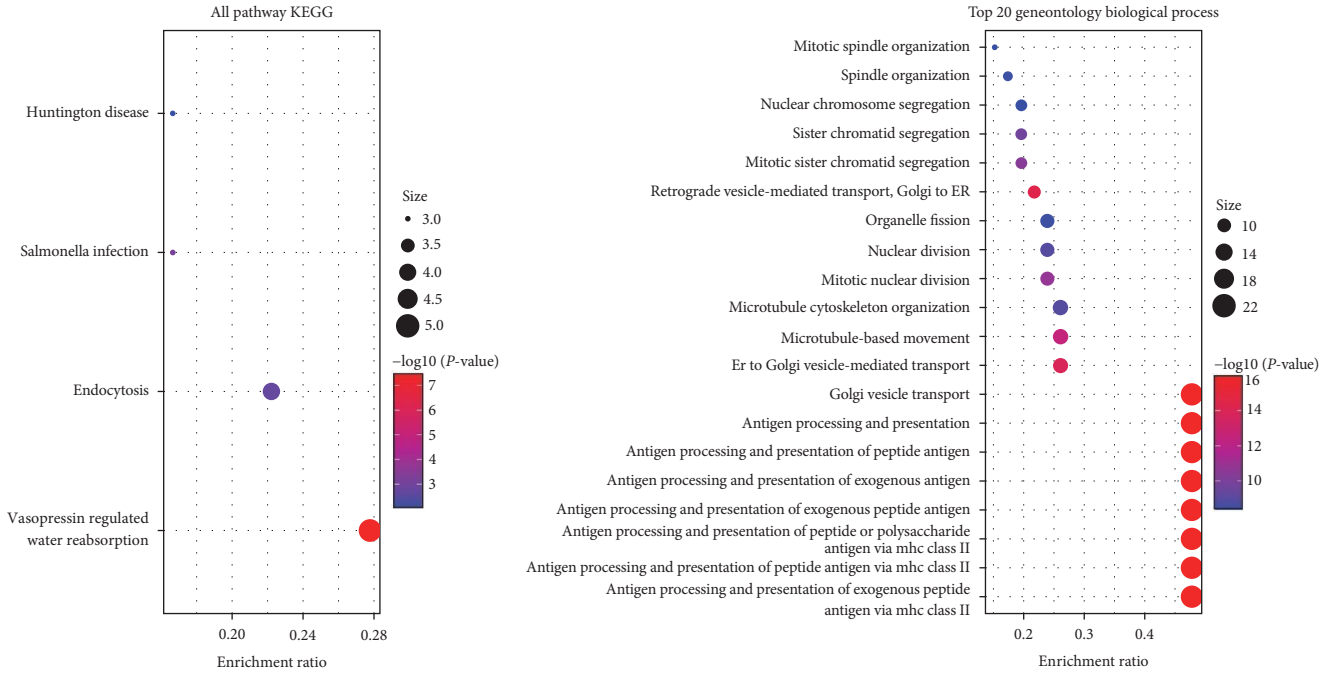


Figure 5: KIF22-related gene enrichment analysis. (a) The gene–gene functional interaction network of KIF22 generated through GeneMania database. (b) The protein–protein interaction network of KIF22 constructed through STRING database. (c) GO analysis (cellular component) of the KIF22 binding proteins. (d) GO analysis (molecular function) of the KIF22 binding proteins. (e) KEGG analysis of the KIF22 binding proteins. (f) GO analysis (biological process) of the KIF22 binding proteins.

level of follicular helper T cell, NK T cell, Th2 CD4+ T cell, and Th1 CD4+ T cell in most tumor types and showed a negative relationship with the infiltration level of endothelial cell, neutrophil, and CD8+ T cell in most malignant neoplasms (Figure 9(a)). Furthermore, KIF22 expression was positively associated with the tumor infiltration of MSDCs, and negatively associated with the tumor infiltration of CAFs and Tregs in most tumors (Figure 9(b)).

The expression level of KIF22 affected prognoses relying on the infiltration of different immune cells. We took CD8+ T cells as an example for further analysis, enriched CD8+ T cells and high KIF22 expression indicated a worse survival probability in patients with KIRC and SARC, while enriched CD8+ T cells and high KIF22 expression indicated a better survival probability in patients with ESCC and UCEC. Furthermore, decreased CD8+ T cells and high KIF22 expression indicated a worse survival probability in patients with LIHC, while decreased CD8+ T cells and high KIF22 expression indicated a better survival probability in patients with OV, STAD, and HNSC. (Figure 9(c)). *Supplementary 9* provides the detailed information. The results above suggested that KIF22 might affect the survival probability of cancer patients partially relying on the infiltration of different immune cells.

3.9. KIF22 Correlates with Therapeutic Response in Multiple Cancer Types. The results analyzed based on the RNAact-Drug database indicated that the methylation, expression, and CNV of KIF22 were closely correlated with drug susceptibility (Figure 10(a) and *Supplementary 10*). The biomarker relevance of KIF22 was evaluated by comparing it with predefined biomarkers according to their predictive power on therapeutic response and survival probability of patients under immune checkpoint blockade treatment. KIF22 had an area under the receiver operating characteristic curve (AUC) of >0.5 in 11 of the 23 ICB subcohorts. The predictive value of KIF22 was higher than B. Clonality, TMB, and T. Clonality, which gave AUC values of >0.5 in 7, 8, and 9 of the 23 ICB subcohorts, respectively (Figure 10(b)). In addition, in patients with kidney cancer and melanoma, ICB therapy showed good treatment outcome when KIF22 expression level was low (Figure 10(c)). Furthermore, KIF22 expression was closely related to treatment outcomes in clinical cancer treatment. Patients with breast cancer that expressed KIF22 at a higher level exhibited resistance to chemotherapy and anthracycline. Patients with ovarian cancer that expressed KIF22 at a higher level were less responsive to chemotherapy and were more responsive to targeted therapy when expressed KIF22 at a lower level. Patients with glioblastoma multiforme that expressed KIF22 at a lower level were more resistant to chemotherapy (Figure 10(d)). These results proved that KIF22 might be selected as a new biomarker for predicting survival probability and treatment outcome.

3.10. KIF22 Coexpression Network. The coexpression network of KIF22 in HNSC was analyzed based on the LinkedOmics database to identify the potential mechanisms that

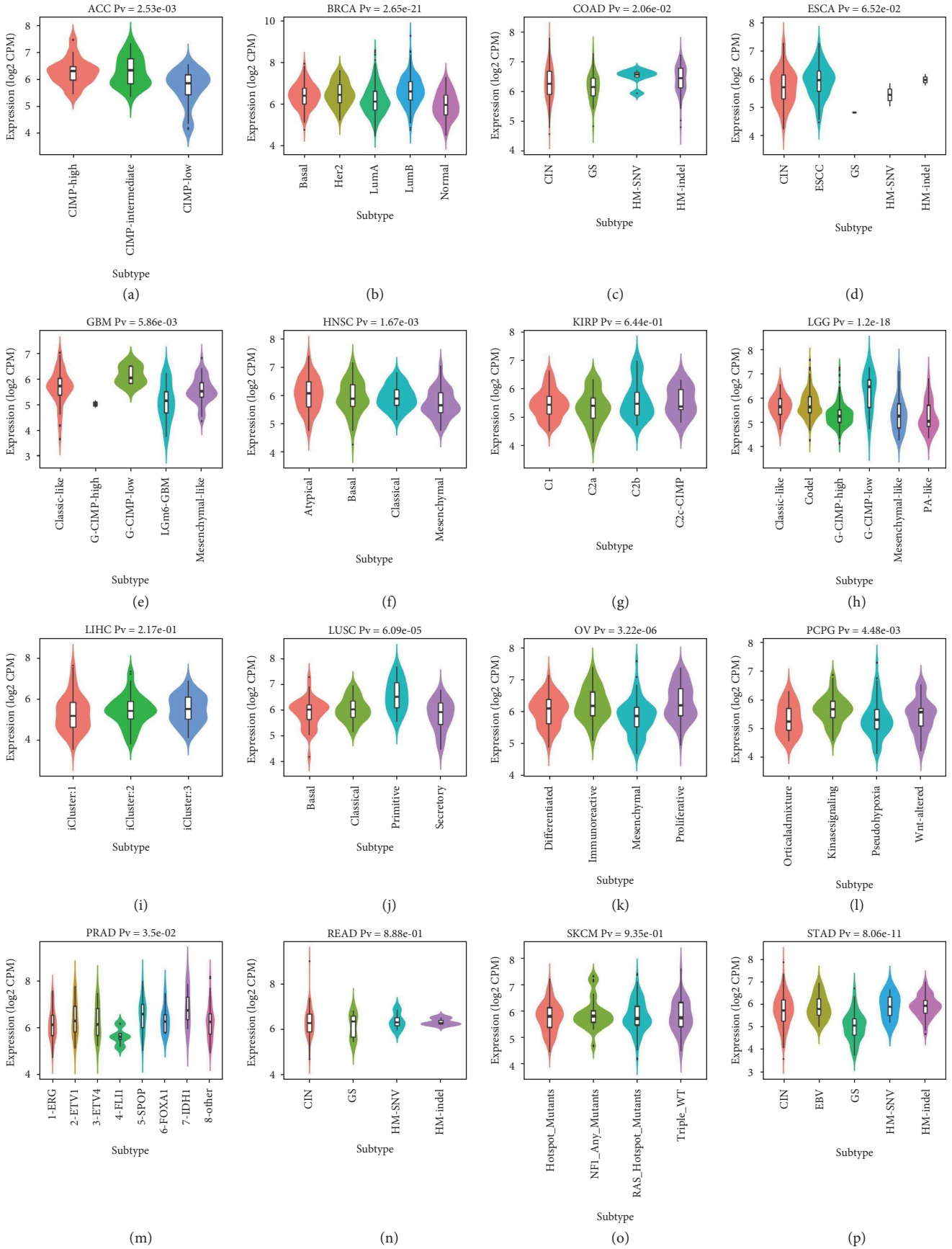


FIGURE 6: The relevance between KIF22 expression level and pan-cancer molecular subtypes.

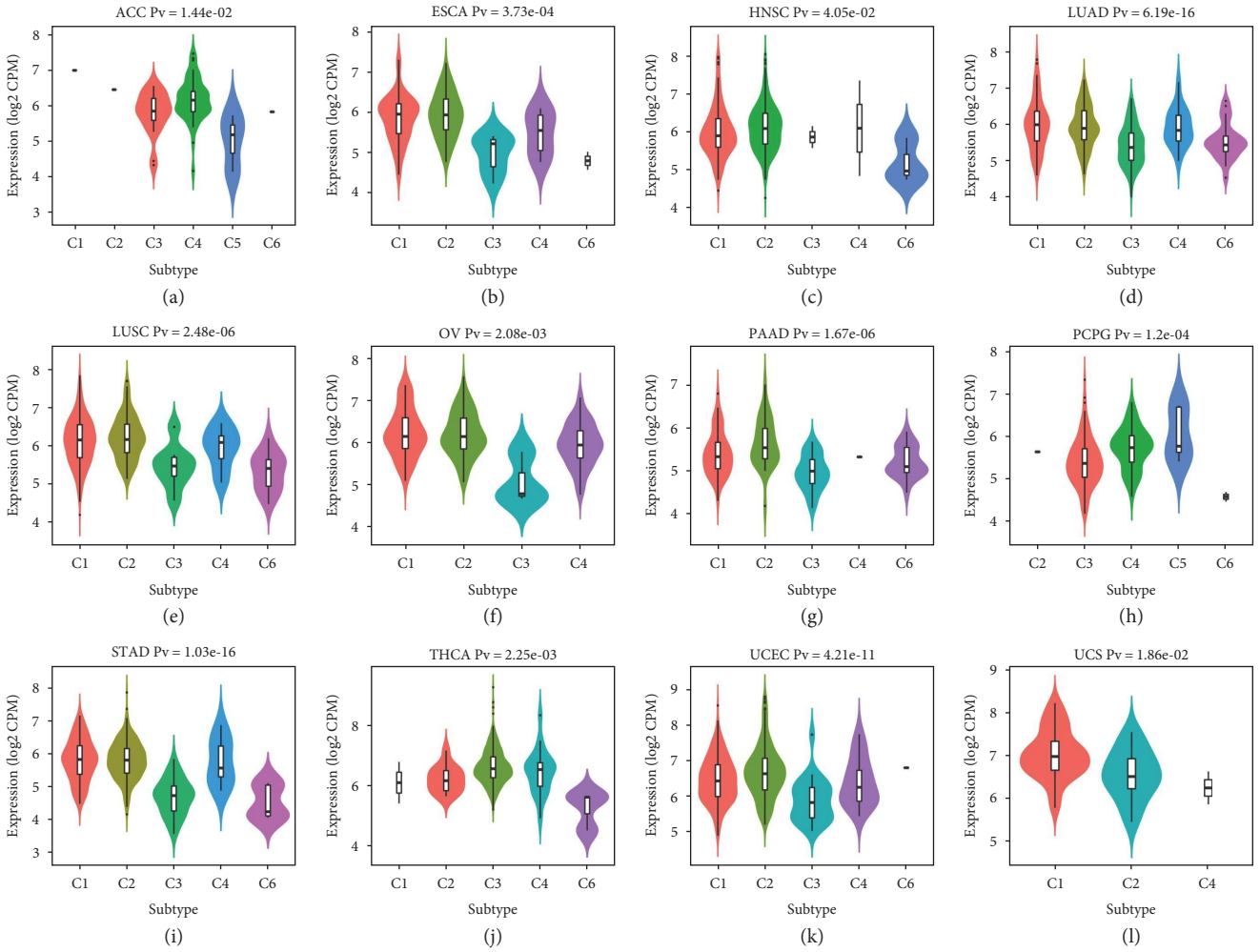
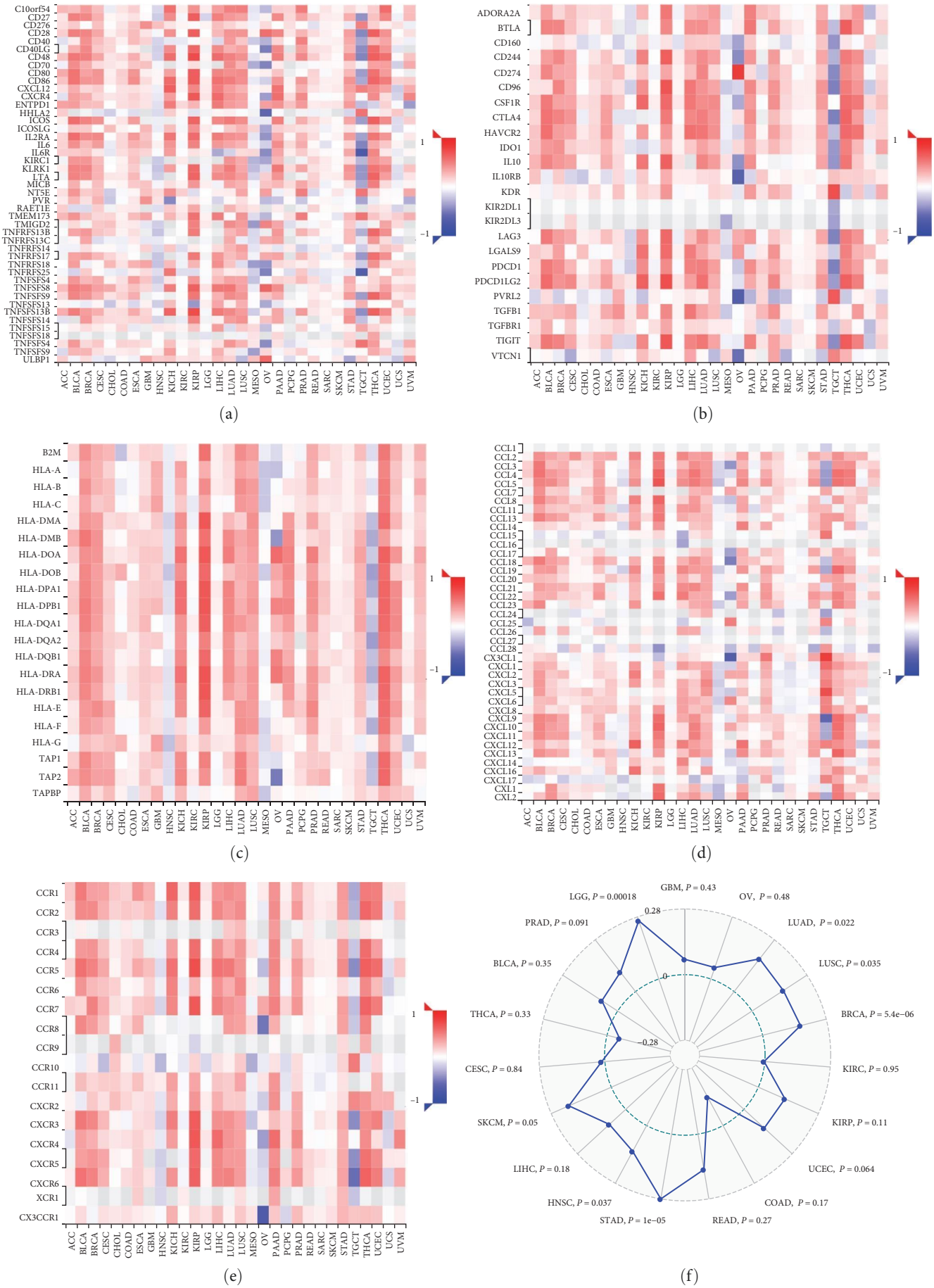


Figure 7: The relevance between KIF22 expression and pan-cancer immune subtypes.

were regulated by KIF22. In HNSC, 7,191 genes showed positive relationship with KIF22, and 6,711 genes showed negative relationship with KIF22 (P-value < 0.05) (Figure 11(a)). The top 50 genes that showed positive and negative relationship with KIF22 were displayed (Figures 11(b) and 11(c)). *Supplementary 11* provides the detailed information. C16orf59, CHTF18, and SNRPA showed the strongest correlation with KIF22 ($r = 0.77$, 0.75, 0.73 and $P = 1.00\text{E-}103$, 5.3E-103, 1.31E-96, respectively). In addition, Gene Set Enrichment Analysis showed that KIF22 and the coexpression genes mainly took part in cell cycle, DNA replication, nucleotide-excision repair, and RNA processing (Figure 11(d)). In addition, the KEGG pathway analysis proved that KIF22 and the coexpression genes were mainly enriched in DNA repair, cell cycle, homologous recombination, and DNA replication (Figure 11(e)). These results provided more evidence that KIF22 might have an important function in human malignancies through manipulating cell cycle and DNA repair.

4. Discussion

KIF22 has been reported to be a member of the kinesin-10 subfamily [17]. Previous studies have reported that KIF22 is a plus-end-directed microtubule-based motor with both DNA- and microtubule-binding domains and is involved in cytoskeletal dynamics, synaptic development, microtubule stability, and chromosome movement [19, 20]. KIF22 deficiency causes the death of about half of $KIF22^{-/-}$ mice embryos. KIF22 presents together with microtubules in the interstices between adjacent anaphase chromosomes and plays an important role in the formation of compact chromosome mass at telophase by holding individual chromosomes together during segregation. KIF22 deficiency results in the loss of compaction of anaphase chromosomes and leads to the formation of micro- or multinucleated cells in early-stage embryos [23]. Emerging evidence revealed that the KIF22 expression level was markedly upregulated in cancer [52–56]. KIF22 was a poor prognostic factor and



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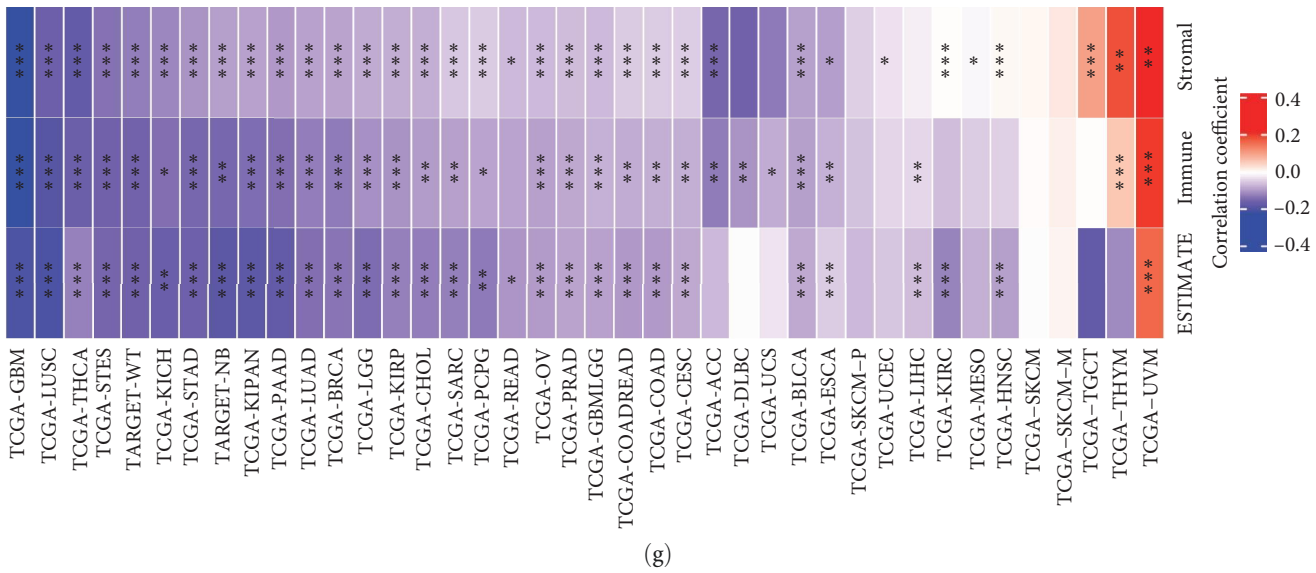


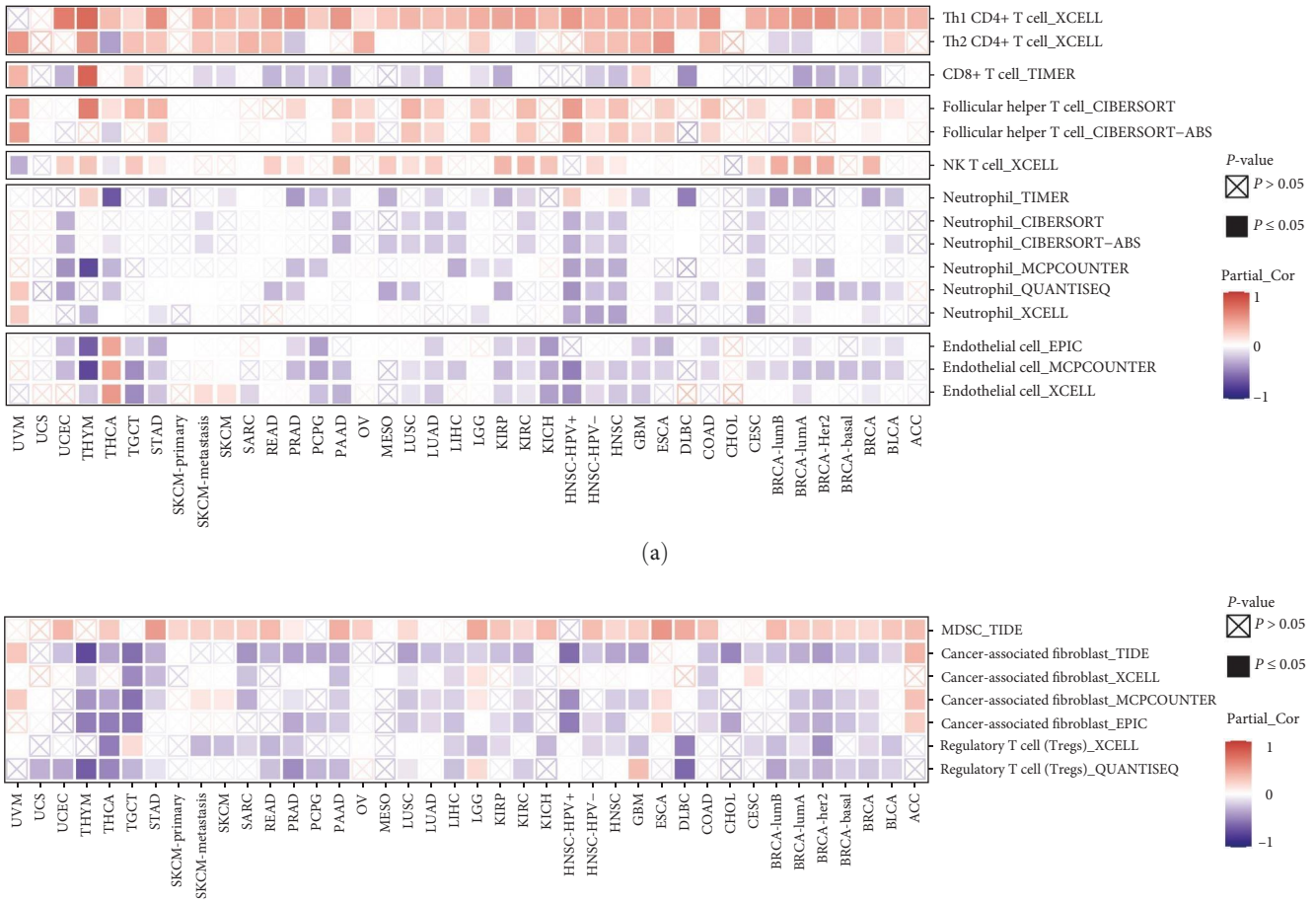
(g)

Figure 8: The relevance between KIF22 and immunomodulators, chemokines, neoantigen, ESTIMATE in different cancer types. (a) The relevance between KIF22 methylation status and immunostimulators. (b) The relevance between KIF22 methylation status and immunoinhibitors. (c) The relevance between KIF22 methylation status and MHC molecules. (d) The relevance between KIF22 methylation status and chemokines. (e) The relevance between KIF22 methylation status and chemokine receptors. (f) The relevance between KIF22 expression and neoantigen. (g) The relevance between KIF22 expression and ESTIMATE. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

was relevant to cancer cell proliferation, migration, and invasion [52, 56]. Nevertheless, specific genes may have different expressions and play different roles in different tumors due to tumor heterogeneity. mRNA and protein expression profiles could help us to identify novel biomarkers for cancer diagnosis, which would facilitate the progress of treatment for different human malignancies [57, 58]. KIF22 expression level was upregulated in most tumors in contrast with nontumorous tissues. High KIF22 expression was associated with worse OS in UCEC, GBMLGG, ACC, LAML, KIRC, ALL-R, LGG, SKCM-M, UVM, ESCA, LIHC, LUSC, SARC, and SKCM. Previous studies also demonstrated that KIF22 expression level was upregulated and correlated with high-risk features in pancreatic cancer, bladder cancer, breast cancer, tongue squamous cell carcinoma, colon cancer, and prostate cancer [13, 52–54, 59, 60]. However, the relevance between KIF22 expression and survival probability in THYM, CESC, OV, HNSC, PCPG, STAD, and THCA suggested that KIF22 exhibited a tumor-specific role in influencing the prognosis of cancer patients.

The clinical and genetic characteristics of cancer are exceedingly variable, varying between people and even between distinct tumor areas [61]. KIF22 expression was positively correlated with genomic heterogeneity in most malignant neoplasms. The heterogeneity characteristics of cancer lead to treatment resistance and recurrence following therapy, resulting in decreased survival probability. Different mutation profiles lead to variability in therapeutic response and variable survival outcomes of patients with different cancers [48]. KIF22 showed variable prognostic roles in different cancer types which might be associated with heterogeneity. Cancer is a multistage process and accumulates lots of chromosomal rearrangements and a great number of mutations [62]. The genetic alterations in the genome were the main driving force for the transition of normal cells to invasive and metastatic malignant neoplasms [63]. Genetic mutation analysis of the cancer-associated genes would bring us valuable insights into the functions of oncogenes in carcinogenesis and tumor development [64]. About 1.8% of cancer patients showed genetic alteration in KIF22. Cancer patients with genetic changes in KIF22 had a better survival rate than patients without mutations, which suggested that KIF22 might serve as the force for driving tumor progression and mutations in KIF22 suppressed its role in tumor progression.

Stemness refers to the ability to differentiate and self-renew cells [65]. New cell subpopulations, which have been reported as stem-like cancer cells or cancer stem cells, have been identified in malignant neoplasms. These cancer stem cells showed high dedifferentiation and stemness characteristics [66, 67]. The tumor stemness showed a close connection with tumor pathology and could be used for predicting clinical outcomes. Our results indicated that KIF22 expression was positively associated with cancer stemness in most malignant neoplasms, but was negatively related to cancer stemness in THYM, KIPAN, PRAD, and THCA. These results were consistent with the prognostic significance of KIF22 in tumors. KIF22 might drive tumor progression and influence the prognosis of cancer patients partially by affecting cancer stemness. Epigenetic modification, especially methylation modification, drew more attentions than genetic changes. Epigenetic modification could influence the initiation as well as the progression of malignant neoplasms [68]. The dysregulation of epigenetic modification in cancer cells frequently leads to gain of stemness characteristics and



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oncogenic dedifferentiation [46, 47]. Methylation modification is one of the major forms of epigenetic modification that regulates the transcription of target genes [69]. The promoter region of KIF22 was hypomethylated in COAD, LIHC, PRAD, TGCT, UCEC, BLCA, and THCA and hypermethylated in KIRC, CESC, SKCM, ESCA, HNSC, BRCA, LUSC, and CHOL compared with normal tissues. The associations between survival probability and methylation level of KIF22 promoter even the methylation level of single CpG island were diverse, which furtherly proved that the methylation modifications in KIF22 promoter showed multidirectional functions in tumor progression.

Tumor is an integrated, diverse, and complex system that is comprised by cancer cells and tumor-associated noncancerous cells [65]. The TME builds an ecology for cancer cell proliferation and survival [65, 70]. KIF22 expression was negatively associated with ESTIMATE in most malignant neoplasms, which suggested that KIF22 might have a positive effect on tumor purity. The TME brings the tumor cells lots of chances for cell–cell interaction and signal transmission to regulate tumor progression, which emphasizes the importance of clarifying the regulation mechanisms of the interaction within the heterogeneous tumor cells even the interaction with noncancerous cells present in the TME [65]. Previous studies have reported that immunomodulators, chemokines, and neoantigen are the main factors that regulate the interaction between cancer cells and noncancerous cells. Our results suggested that the expression level of KIF22 was positively associated with neoantigen in LUAD, LUSC, BRCA, STAD, HNSC, and LGG. In addition, KIF22 methylation status was positively correlated with MHC molecules, immunoinhibitor, chemokines, immunostimulator, and chemokine receptors in most cancers. These results implied that KIF22 might take part in organizing the TME by coordinating the immunomodulators, chemokines, and neoantigen. Previous studies indicated that elevated expression of KIF22 might affect the response of melanoma cells to promigratory cues in the tumor microenvironment [71]. Our results indicated that KIF22 showed no dramatic correlations with immunomodulators, chemokines, and ESTIMATE in SKCM. However, KIF22 was positively related to tumor infiltration of Th2 CD4+ T cell, Th1 CD4+ T cell, and myeloid-derived suppressor cell and negatively related to tumor infiltration of Tregs and CD8+ T cells in cutaneous melanoma. More further studies might need to be carried out to confirm the roles and underlying mechanisms of KIF22 in tumor microenvironment.

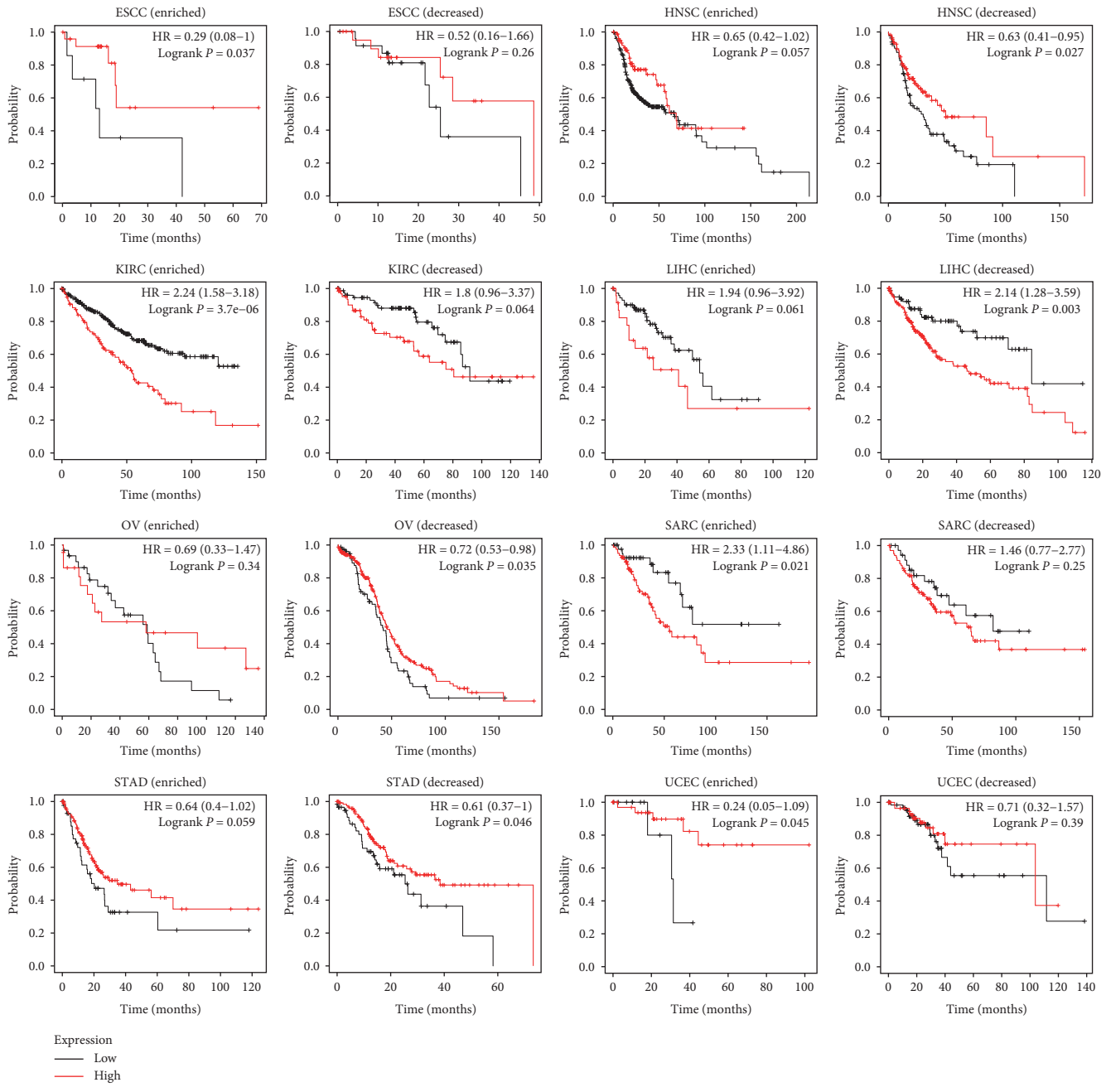

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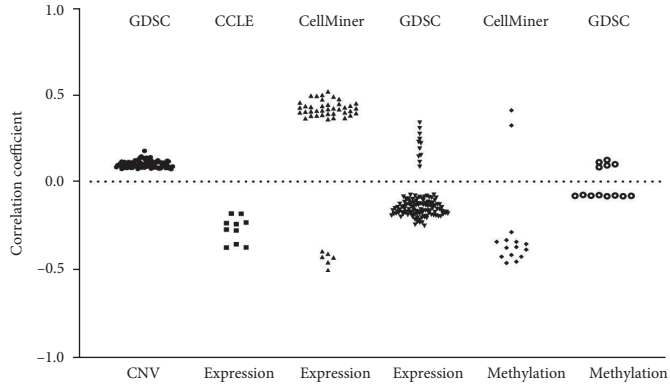
Figure 9: The association between KIF22 expression level and tumor immune infiltration. (a) The relationship between KIF22 expression level and the infiltration level of Th1 CD4+ T cell, NK T cell, Th2 CD4+ T cell, follicular helper T cell, CD8+ T cell, neutrophil, and endothelial cells in different tumors. (b) The relevance between KIF22 expression level and the infiltration level of CAFs, MDSCs, and Tregs in different tumors. (c) Kaplan–Meier survival curves indicated the association between OS and KIF22 expression level in different CD8+ T cell subgroups.

Numerous studies showed that the abundance and composition of tumor-infiltrating immune cells in the tumor microenvironment could serve as independent predictors for survival rate, therapeutic efficiency, and treatment outcome [72]. Previous studies proposed two distinct explanations for tumor immune evasion. First, the infiltration of tumor-infiltrating lymphocytes in the TME resulted in the dysfunction of T-cell and T-cell anergy, which facilitated the escape of tumor cells from the immune system of the host [73]. Second, tumor prevented the infiltration of tumor cytotoxic lymphocytes based on the tumor-infiltrating immunosuppressive cells, such as MDSCs, Tregs, and CAFs, which have been reported as biomarkers for T-cell exclusion in malignant neoplasms [74]. Our results indicated that KIF22 showed a



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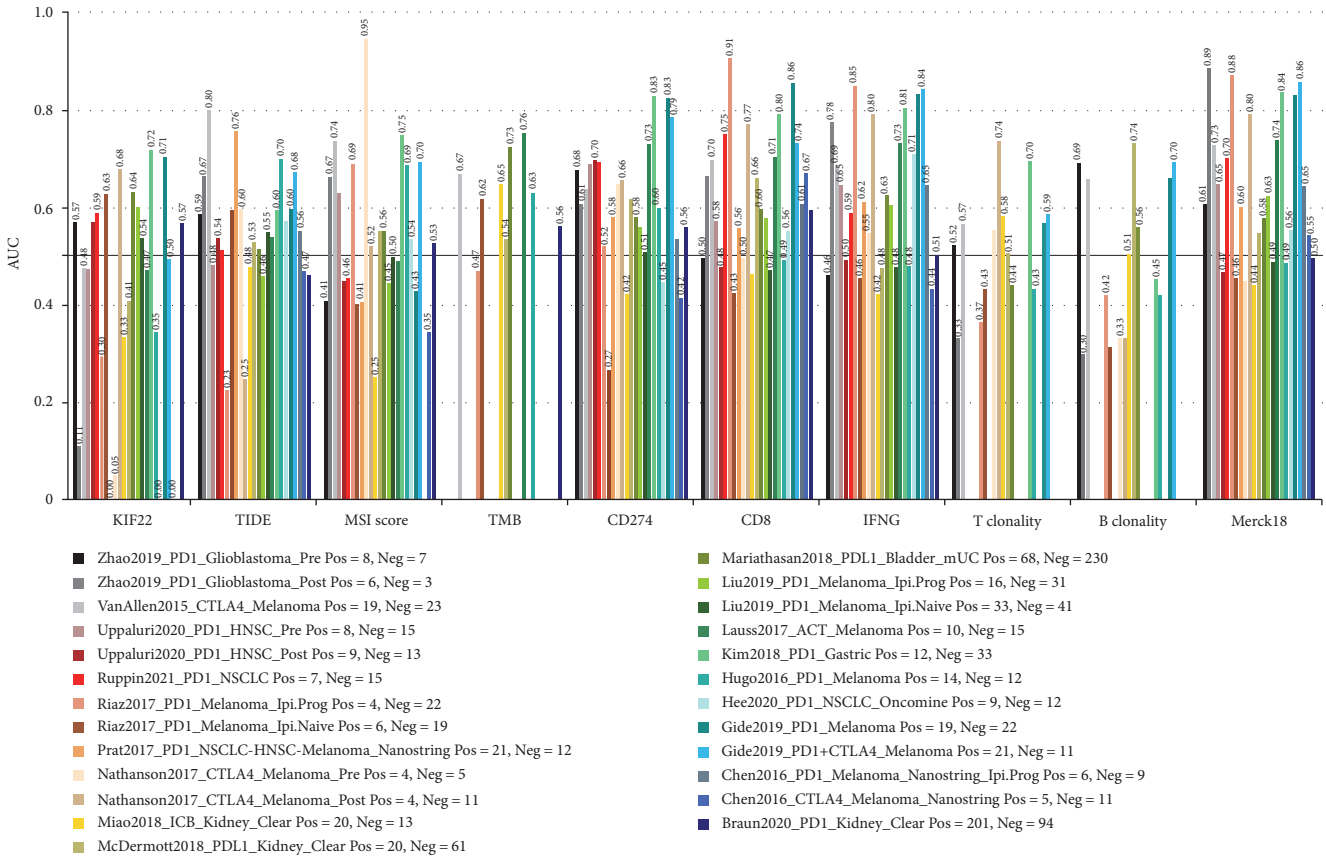

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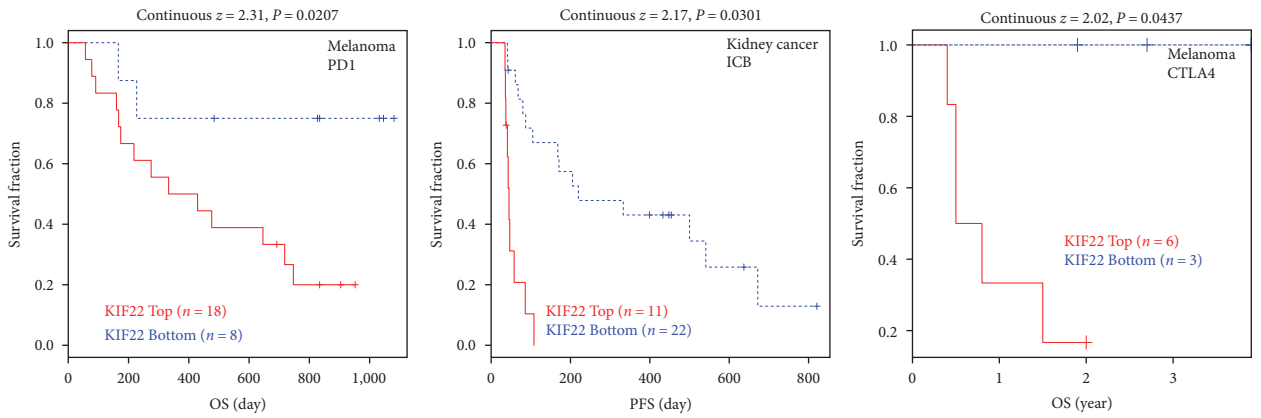

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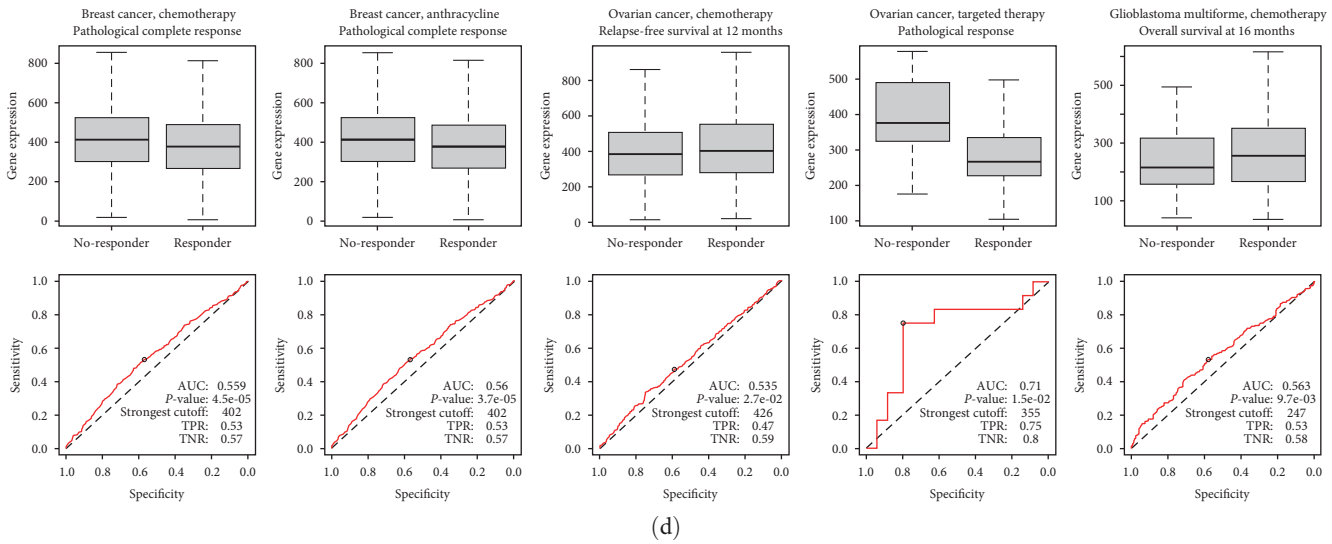


(d)

FIGURE 10: The association between KIF22 and therapy outcome in different cancers. (a) The relationship between drug susceptibility and the expression, methylation, CNV of KIF22. (b) The biomarker relevance of KIF22 compared with predefined tumor immune response biomarkers in ICB subcohorts. (c) Kaplan–Meier survival curve of ICB subcohorts with different KIF22 expression levels. (d) The relevance between KIF22 expression level and response to chemotherapy in ovarian cancer, glioblastoma multiforme and breast cancer cohorts, targeted therapy in ovarian cancer cohorts, and anthracycline therapy in breast cancer cohorts.

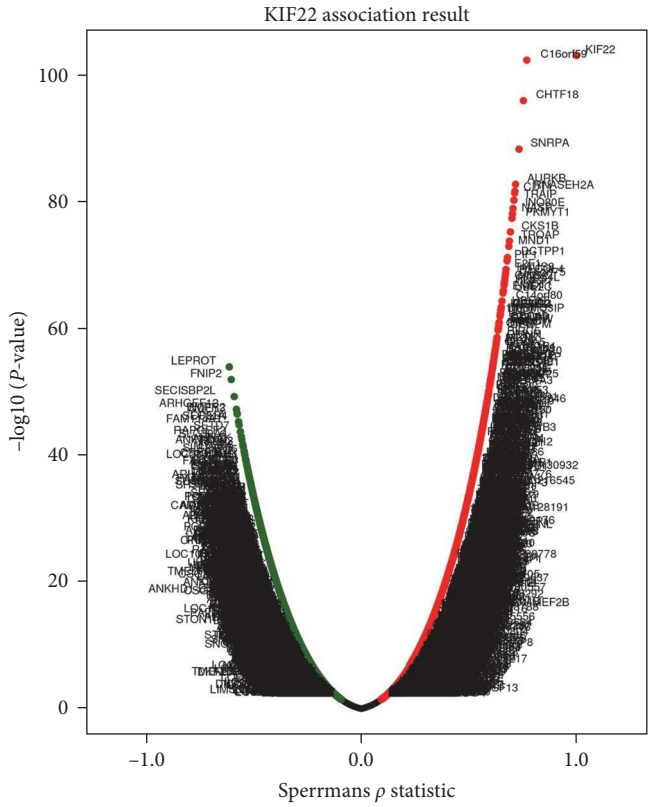
positive relationship with the infiltration level of MDSCs and Th1 CD4+ T cells in most malignant neoplasms. Myeloid-derived suppressor cells inhibited the number and function of DC and T cell and facilitated tumor progression [75]. The presence of IL-12 and IFNγ drove the differentiation of precursor CD4+ T cells into Th1 cells. Th1 cells produced IFNγ and LT (TNFβ) and regulated cell-mediated inflammatory reactions [76]. KIF22 might regulate tumor immune evasion dependent on the tumor-infiltrating MDSCs and Th1 CD4+ T cells in the TME.

Immune checkpoint inhibitors can reverse the damaged antitumor immune response of tumor-infiltrating lymphocytes and trigger antitumor characteristics of tumor-infiltrating T cells by blocking the immunosuppressive receptors [77]. Antibodies against PD-L1 or PD-1 effectively treat a variety of tumors and exhibit better clinical benefits [78]. Our results suggested that KIF22 could be selected as a new biomarker for tumor immune evasion. Melanoma and kidney cancer patients that expressed KIF22 at a lower level had a better survival probability under PD-1 and CTLA-4 ICB therapy, which meant that KIF22 was an important factor for predicting the immunotherapy outcome. In addition, KIF22 could be selected as a new biomarker for predicting the efficacy of targeted therapy and chemotherapy. Patients with glioblastoma or ovarian cancer that expressed KIF22 at a lower level had a poor chemotherapy outcome. On the contrary, patients with breast cancer and higher KIF22 expression were insensitive to chemotherapy and patients with ovarian cancer and higher KIF22 expression were resistant to targeted therapy. These studies implied that KIF22 might function in different cancer types via different signal pathways. KIF22 might exert a positive or negative influence on these strategies via different signal pathways in different cancer types, which probably contributes to the variation in clinical outcomes.

The present study improves our understanding of KIF22 potential function in carcinogenesis and cancer progression, but there are still several limitations in our study. First, most of the analyses in this study were performed based on mRNA levels of KIF22. Due to the deficiency of KIF22 protein expression data, the analyses based on KIF22 protein levels were imperfect. A deeper analysis, based on KIF22 protein levels, would make the results more convincing. Second, most of the conclusions were drawn based on bioinformatic analysis. Therefore, the current study lacked validation of clinical specimens and biological experiments, and more basic and clinical research were needed to validate these results.

5. Conclusion

KIF22 expression was upregulated in tumors than noncancerous tissues and was closely related to tumor stemness, prognosis, genomic heterogeneity, neoantigen, ESTIMATE, and infiltration of immune cells in the TME. The KIF22 methylation status was correlated with immunomodulators and chemokines. KIF22 showed strong relationships with drug susceptibility and could serve as a new biomarker for prognosis and treatment outcomes. KIF22 interacting and cofunctional partners were mainly involved in DNA repair, cell division, cell cycle, and antigen processing and presentation. KIF22 could be selected as a new biomarker for clinical diagnosis, therapeutic schedule, prognosis, and cancer monitoring.



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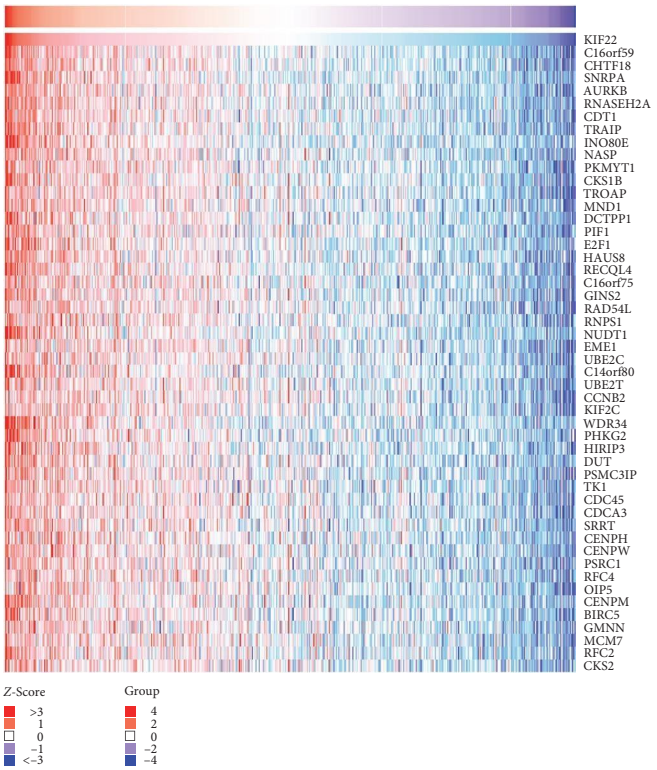

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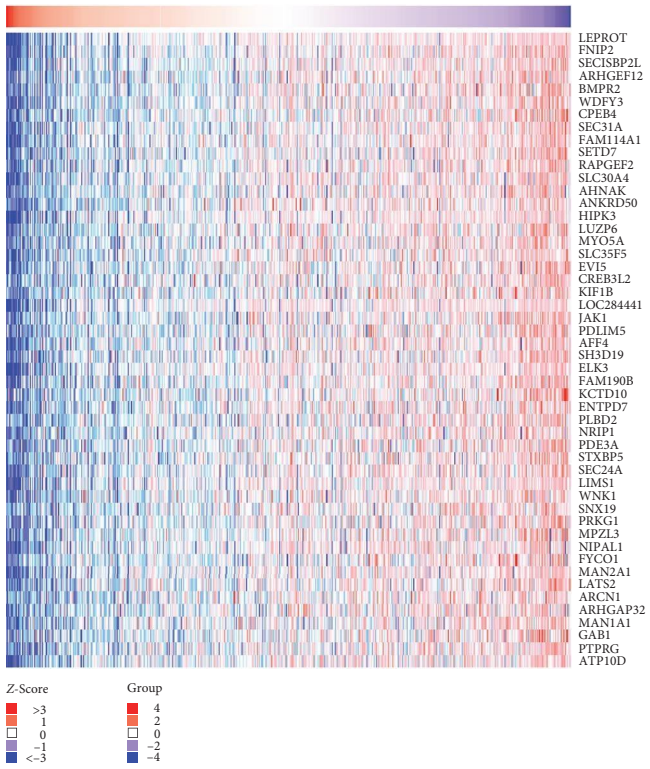

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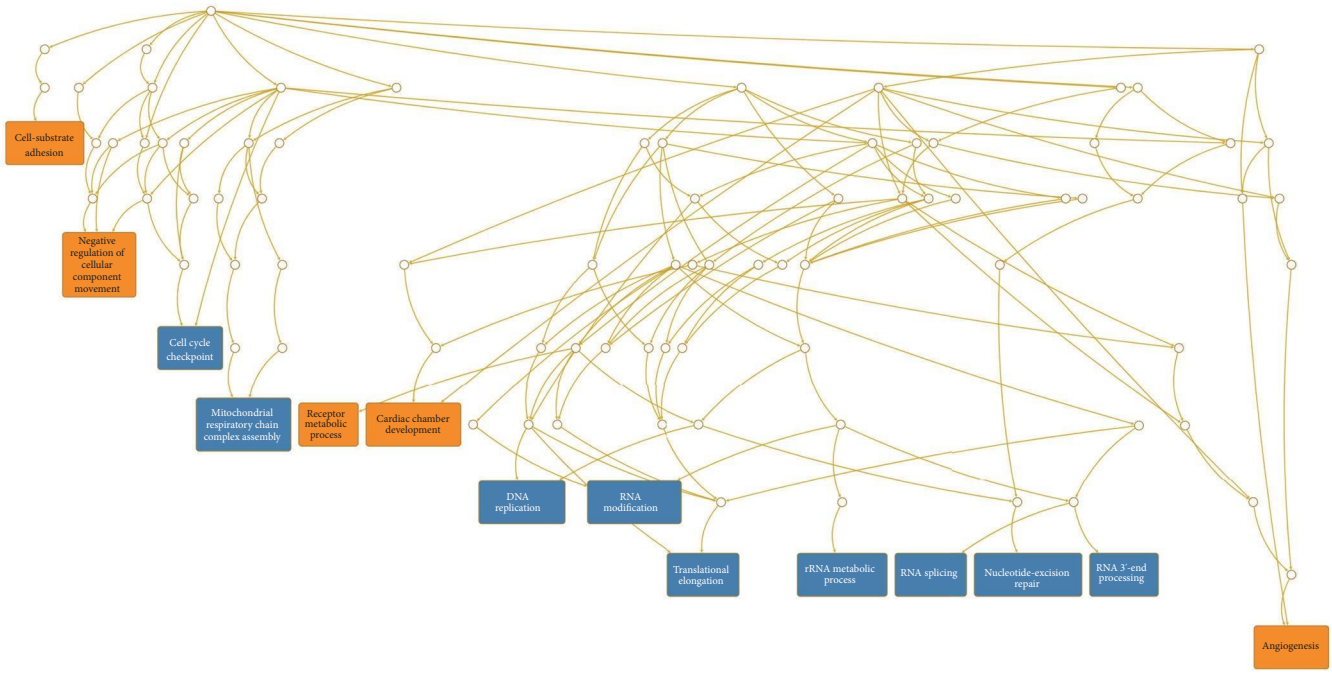

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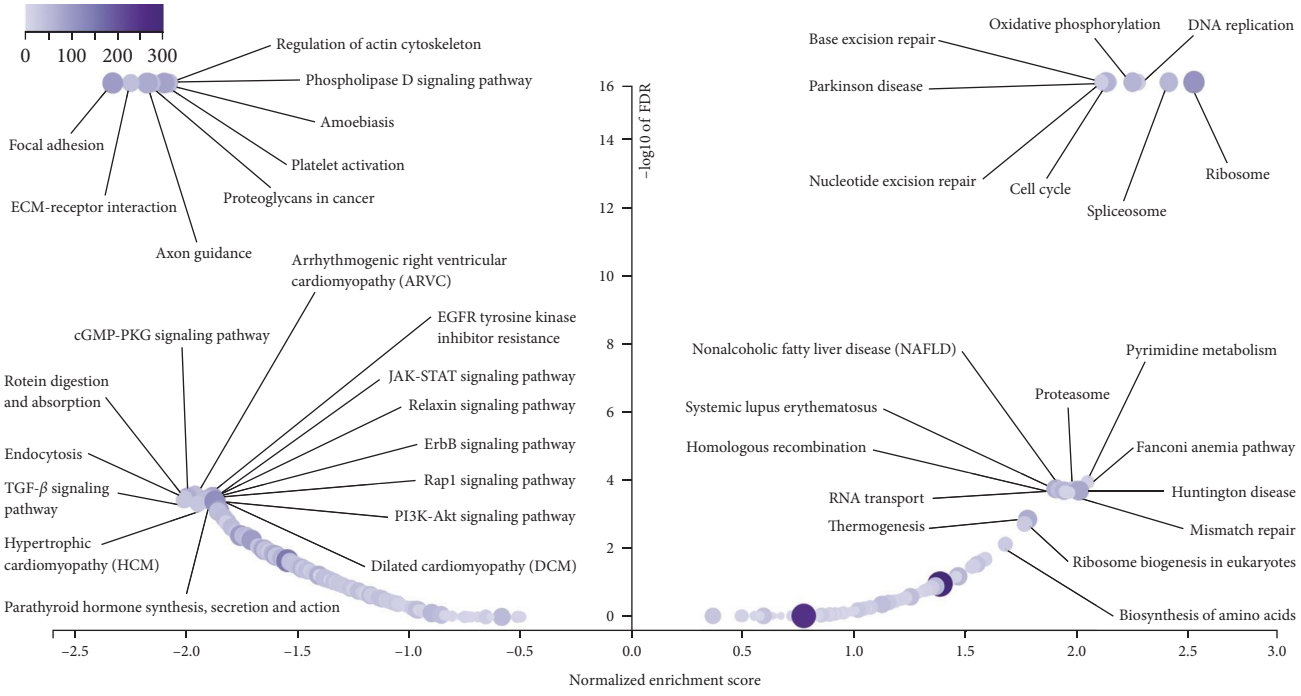

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Figure 11: The coexpression genes of KIF22 in HNSC. (a) KIF22 coexpression genes in HNSC. (b) The top 50 KIF22 positively correlated genes in HNSC. (c) The top 50 KIF22 negatively correlated genes in HNSC. (d) GO analysis (biological process) of the KIF22 coexpression genes. (e) KEGG analysis of the KIF22 coexpression genes.

Data Availability

Part of the original data can be obtained from TGGA, GEPIA, and other databases. Other datasets generated or analyzed during the current study were included in the article and supplementary materials.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Xiuhong Guo: Investigation, data curation, validation, visualization, writing original draft, writing-review and editing. Huayue Cao: Validation, visualization, writing-review and editing. Yuening Wu: Validation and visualization. Mei Hu: Writing-review and editing. Jingxiang Li: Project administration, writing-review and editing.

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Supplementary Materials

Supplementary 1. Abbreviations.

Supplementary 2. Expression profile of KIF22 in different tumors and noncancerous tissues. (a) KIF22 expression profile in different tumors and noncancerous tissues based on the SangerBox database. $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$. (b) KIF22 mRNA expression in different normal tissues. (c) KIF22 mRNA expression in different cell lines. (d) The relevance between KIF22 expression and cell cycle progression.

Supplementary 3. KIF22 expression level in tumor-infiltrating immune cells from various cancer TMEs analyzed through the TISCH database.

Supplementary 4. KIF22 expression profile in various cell types from multiple cohorts analyzed by the TISCH database.

Supplementary 5. Survival probability of different cancer patients with high and low KIF22 expression.

Supplementary 6. The relevance between KIF22 expression level and prognosis of patients with different malignant neoplasms investigated via the PrognoScan database.

Supplementary 7. The relevance between the methylation status of single CpG island in KIF22 promoter and survival probability of patients with different tumors.

Supplementary 8. The relevance between KIF22 expression level and immune subtypes in different tumors.

Supplementary 9. Prognostic significance of KIF22 mRNA expression on the basis of different immune cell subgroups.

Supplementary 10. The relevance between drug susceptibility and the expression, CNV, and methylation of KIF22.

Supplementary 11. The coexpression genes of KIF22 in the HNSC cohort.

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