



Multi-omics Analysis of NUDT19 Across Cancer Types and Its Functional Role in Leukemia*

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Abstract Objective Recent studies have highlighted the critical role of NUDT19 in the initiation, progression, and prognosis of specific cancer types. However, its involvement in pan-cancer analysis has not been fully characterized. This study aims to systematically explore the expression patterns, clinical significance, and immune-related functions of NUDT19 in various cancer types through multi-omics analysis, further revealing its potential role in cancer, particularly its functional and therapeutic target value in leukemia. **Methods** To achieve this goal, various bioinformatics approaches were employed to evaluate the expression patterns, clinical significance, and immune-related functions of NUDT19 in tumors and normal tissues. Additionally, we analyzed the mutation characteristics of NUDT19 and its relationship with epigenetic modifications. Using the single-cell analysis tool SingleCellBase, we explored the distribution of NUDT19 across different cell subpopulations in tumors. To validate these findings, qRT-PCR was used to measure NUDT19 expression levels in specific tumor cell lines, and we established acute myeloid leukemia (AML) cell lines (HL-60 and THP-1) to conduct NUDT19 knockdown and overexpression experiments, assessing its effects on leukemia cell proliferation, apoptosis, and invasion. **Results** Pan-cancer analysis revealed the dysregulated expression of NUDT19 across multiple cancer types, which was closely associated with poor prognosis, clinical staging, and diagnostic markers. Furthermore, NUDT19 was significantly correlated with tumor biomarkers, immune-related genes, and immune cell infiltration in different cancers. Mutation analysis showed that multiple mutations in NUDT19 were significantly associated with epigenetic changes. Single-cell analysis revealed the heterogeneity of NUDT19 expression in cancer cells, suggesting its potentially diverse functional roles in different cell subpopulations. qRT-PCR experiments confirmed the significant upregulation of NUDT19 in various tumor cell lines. In AML cell lines, NUDT19 knockdown led to reduced cell proliferation and invasion, with increased apoptosis, while NUDT19 overexpression significantly enhanced cell proliferation and invasion while reducing apoptosis. **Conclusion** This study demonstrates the diverse roles of NUDT19 in various cancer types, with a particularly prominent functional role in leukemia. NUDT19 is not only associated with tumor initiation and progression but may also influence cancer progression through the regulation of immune microenvironment and epigenetic mechanisms. Our research highlights the potential of NUDT19 as a therapeutic target, particularly for targeted therapies in malignancies such as leukemia, with significant clinical application prospects.

Key words NUDT19, pan-cancer, immunotherapeutic, single-cell analysis

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Globally, cancer is the second leading cause of mortality^[1]. According to the most recent data from the International Agency for Research on Cancer (IARC), it was estimated that around 20 million new cancer cases and 9.7 million cancer-related deaths would occur in 2022^[2]. Early detection and effective treatment notably enhance the survival rates of many malignancies^[3-4]. The identification of tumor

biomarkers offers innovative approaches for early detection and personalized treatment selection, with

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the potential to enhance survival rates and reduce treatment costs^[5-6]. However, the limitations of single-cancer studies have constrained our comprehensive understanding of the diverse aspects and intrinsic mechanisms of target genes. Pan-cancer analysis of genes has become a practical approach for deciphering the complex genetic underpinnings of cancer, providing a broader background and theoretical framework for research in individual cancer types, including leukemia.

Leukemia, particularly acute myeloid leukemia (AML), poses a significant clinical challenge. As the most common acute leukemia in adults, AML accounts for 80% of adult acute leukemias and has a 5-year survival rate of <30% despite intensive chemotherapy^[7-8]. AML's heterogeneity, rapid relapse, and resistance to therapy highlight the urgent need for novel molecular targets^[9]. Targeting the molecular underpinnings of leukemia has become crucial for developing more effective therapies, and understanding the roles of key genes in its pathogenesis is essential^[10]. In this regard, nucleoside diphosphate-linked moiety X motif 19 (NUDT19) has garnered attention as a potential molecular target in various cancers, including leukemia.

NUDT19, also known as RP2, belongs to the Nudix hydrolase family. Several studies have demonstrated that NUDT19 participates in cellular energy metabolism, gene expression regulation, cell signaling, immune regulation, and other critical biological functions^[11-15]. NUDT19 has been implicated in cancers, including hepatocellular carcinoma and prostate cancer. In hepatocellular carcinoma, NUDT19 expression closely correlates with hepatic lipid metabolism, cell proliferation, and the epithelial-mesenchymal transition (EMT) process^[16]. Additionally, NUDT19 has been linked to the pathological advancement of prostate cancer, potentially governing cellular proliferation and the spread of cancerous cells^[17]. These findings suggest NUDT19 may act as a conserved oncogene in diverse cancers. However, its role in specific leukemia types, especially AML—a highly aggressive subtype with poor prognosis—remains underexplored.

This study integrates a pan-cancer analysis of NUDT19, exploring its expression patterns, immune relevance, mutation status, and functional enrichment across various cancers. Building on this, we focus specifically on its role in leukemia, particularly AML,

by validating bioinformatics findings through NUDT19 overexpression and knockdown experiments in leukemia cell lines. By linking the broader findings from pan-cancer analysis to specific leukemia mechanisms, this work provides a deeper understanding of NUDT19's function in AML and other cancers, offering potential directions for future therapeutic strategies, particularly for AML patients.

1 Materials and methods

1.1 Comparison of differential expression of NUDT19 between cancerous and corresponding normal tissues

We utilized a variety of methods to examine the differences in NUDT19 expression levels between cancerous tissues and their corresponding healthy counterparts. We first employed Timer 2.0 to investigate NUDT19 expression in both tumor and normal tissues^[18-20]. Following that, we used Sangerbox 3.0 to explore the expression patterns of NUDT19 in tumor tissues and their corresponding normal counterparts. Utilizing the ggradar package in the R language, we generated a radar map illustrating the variation in NUDT19 expression between tumor and normal tissues. The function “pan_paired_boxplot” generates paired boxplots comparing tumor and normal tissue samples across 23 The Cancer Genome Atlas (TCGA) Program cancers.

1.2 Relevance analysis of NUDT19 expression with prognostic implications and clinical staging

We conducted a relevance analysis of NUDT19 expression with prognostic implications and clinical staging. Forest plots of survival metrics, including overall survival (OS), disease specific survival (DSS), disease free interval (DFI) and progression free interval (PFI) were generated using Sangerbox 3.0 to explore the prognostic significance. Additionally, we explored the association between NUDT19 expression and distinct pathological stages across 33 prevalent cancer types through the utilization of Sangerbox 3.0.

1.3 Relevance analysis between NUDT19 expression with receiver operating characteristic (ROC) curve

To evaluate the diagnostic efficacy of NUDT19, we assessed the area under the ROC curves (*AUC*) across diverse cancer types. An *AUC* value exceeding 0.9 indicates excellent predictive accuracy, while an

AUC between 0.9 and 0.7 suggests a moderate level of predictive accuracy. The ROC curves and their corresponding *AUC* values were generated using the Xiantao Academic Tool.

1.4 Analysis of the correlation of NUDT19 with tumor biomarkers, immune-related genes and immune cell infiltration

An analysis was conducted to investigate the relationship between NUDT19 and tumor biomarkers, including tumor mutation burden (TMB), mutant-allele tumor heterogeneity (MATH), microsatellite instability (MSI) and neoantigen (NEO), alongside immune-related genes. This comprehensive analysis was performed using Sangerbox 3.0. Furthermore, we examined the relationship between NUDT19 and immune cell infiltration using the same tool, Sangerbox 3.0.

1.5 Analysis of NUDT19 gene mutations and correlation between NUDT19 and epigenetic factors

We utilized SANGERBOX 3.0 to analyze the mutations in *NUDT19* and investigate the correlation between *NUDT19* and RNA modification genes. Additionally, we assessed the correlation between *NUDT19* and methylation transferase using Timer 2.0.

1.6 Construction of protein-protein interaction (PPI) networks and enrichment analysis

We constructed a PPI network diagram of NUDT19 using the String platform. Next, the PPI network was refined and analyzed with Cytoscape to identify the 5 most critical genes within the network. For elucidating the biological functions and associated pathways of the genes of interest, we employed the Metascape database for annotation and visualization. This process included performing gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis on the differentially expressed genes. Statistical significance was defined based on a minimum overlap of ≥ 3 and a threshold of $P \leq 0.01$. This rigorous criterion ensured robust and reliable results in identifying enriched biological processes and pathways associated with the studied genes.

1.7 Single-cell analysis of NUDT19

We made use of the scCancerExplorer platform (<https://bianlab.cn/scCancerExplorer/home>) to examine the immune cell composition within tumor tissue and the distribution pattern of NUDT19^[21].

1.8 Cell culture

Cell lines obtained from the Shanghai Cell Bank were employed. T24, NCM460, QSG7001, DU145, GES-1, SGC-7901, HS-5, HL-60 and THP-1 cell lines underwent culture in RPMI 1640 medium alongside 1% penicillin/streptomycin and 10% fetal bovine serum (FBS) at 37°C with 5% CO₂. HepG2 and BEAS2B cells were cultured under identical conditions in DMEM with high glucose medium. SV-HUC-1, SW1116, Calu-3, and RWPE-1 cells were cultured in F12K medium, L-15 medium, MEM, and K-SFM medium, respectively, each supplemented with 1% penicillin/streptomycin and 10% FBS at 37°C with 5% CO₂.

1.9 siRNA transfection method

To knock down *NUDT19* gene expression, specific siRNAs targeting *NUDT19* were designed and synthesized. AML cell lines were transfected with the siRNAs using Lipofectamine® 2000 transfection reagent (Thermo Fisher Scientific) according to the manufacturer's instructions. After transfection, cells were cultured for 24 h before protein extraction and subsequent Western blot analysis.

1.10 Overexpression vector transfection method

To achieve overexpression of the *NUDT19* gene, AML cell lines were transfected with an overexpression vector containing *NUDT19* gene (pcDNA3.1-NUDT19) using Lipofectamine® 3000 (Thermo Fisher Scientific). After transfection, the cells were cultured for 24 h before protein extraction and subsequent Western blot analysis.

1.11 Quantitative reverse transcription PCR (qRT-PCR)

Adhering to the protocols outlined in the PrimeScript RT Reagent Kit (TaKaRa, Japan), RNA extraction was performed using Trizol, followed by reverse transcription. Subsequently, PCR reactions were conducted utilizing the SYBR Premix Ex Taq Kit (TaKaRa, Japan), in strict accordance with the manufacturer's instructions. The primer sequences utilized are detailed below. NUDT19 F: AGGAAG-GCAAGCAGTTTCAC, R: ATACTTTGGCTGAAC-AGTCACG; GAPDH F: TGTGTGGAGAGAAGC-AAACCA, R: TTAACACCATTTTGCATCGAAGA.

1.12 Western blot

During the cell collection phase, AML cell lines from the empty vector control group, NUDT19 overexpression group, and siRNA knockdown group

were processed separately. Cells were collected 48 h after transfection. The cells were rinsed twice with PBS to eliminate any remaining culture medium, then lysed with RIPA buffer containing protease inhibitors at 4°C for 20–30 min, with occasional gentle mixing. The lysates were subsequently centrifuged at 12 000 r/min for 10 min, and the supernatants were carefully collected. Protein concentration was quantified using a BCA protein assay kit, providing the necessary data for the subsequent Western blot analysis. For gel preparation, 10% separating gel and 5% stacking gel were chosen based on the molecular weight of the target protein. A 20 µg protein sample was loaded into each well for SDS-PAGE electrophoresis, with a pre-stained protein marker used as a molecular weight reference. Electrophoresis was carried out at 80 V for the stacking gel and at 120 V for the separating gel. After electrophoresis, proteins were transferred to a nitrocellulose (NC) membrane using a Bio-Rad semi-dry transfer system at 10 V for 2 h. Following transfer, the NC membrane was incubated with blocking solution (without serum) for 30 min at room temperature on a shaker. Following blocking, the membrane was quickly rinsed with TBST. The primary antibody (2 µl) was diluted 1 : 1 000 in TBST and incubated overnight at 4°C with gentle agitation. The following day, the membrane was washed four times with TBST, each wash lasting 10 min. It was then incubated with a secondary antibody, diluted 1 : 10 000, at room temperature for 1 h. After washing 4 times, the membrane was treated with ECL chemiluminescence reagent, and protein bands were detected using a Tanon imaging system.

1.13 CCK-8 assay

AML cell lines (HL-60, THP-1) transfected with NUDT19 expression plasmids or siRNA were plated in 96-well plates at a density of 5×10^3 /well, ensuring a minimum of 5 replicate wells for each group. Blank controls (without cells, but with culture medium) and negative controls (cells transfected with empty vector plasmid) were also included. The cells were incubated at 37°C in a 5% CO₂ environment. Cell viability was evaluated every 24 h for a duration of 72 h. At every time interval, 10 µl of CCK-8 solution was introduced into each well, followed by gently shaking the plate to ensure thorough mixing. Following a 2-h incubation, the absorbance (*A*) at 450 nm was recorded with a microplate reader. The *A*₄₅₀ values were recorded and

used to generate cell proliferation curves, allowing for statistical comparison of proliferation differences across experimental groups.

1.14 Transwell cell invasion assay

For the transwell cell invasion assay, a 1 : 30 dilution of Matrigel (9.1 g/L) in PBS was prepared, and 100 µl of the diluted solution was placed into the upper chamber of each transwell insert, while 500 µl of complete culture medium was added to the lower chamber. The plates were kept at 37°C for 1 h to facilitate gel polymerization. Cells from both the experimental and control groups were rinsed twice with PBS, treated with trypsin, centrifuged, and then resuspended in serum-free medium at a concentration ranging from 5×10^4 cells per 200 µl. A 200 µl volume of the cell suspension was added to the upper chamber, and the plates were incubated at 37°C in a 5% CO₂ atmosphere for 24 h. Following incubation, the inserts were rinsed twice with PBS, and non-invading cells on the upper membrane surface were gently scraped off using a cotton swab. The inserts were subsequently fixed with either methanol or 4% paraformaldehyde for 30 min, rinsed twice with PBS, and then stained by immersing them in the lower chamber containing 500 µl of Giemsa stain solution for 10 min. Any excess stain was removed by rinsing the membranes 3–5 times with distilled water, after which the membranes were air-dried. For analysis, the membranes were captured using an inverted microscope, and the cells in 10 randomly chosen fields were counted to assess invasion.

1.15 Statistical analysis

In this study, statistical significance was indicated using *, **, *** and **** to represent significance levels of $P < 0.05$, $P < 0.01$, $P < 0.001$, and $P < 0.0001$, respectively. A significance level of $P < 0.05$ was considered as meeting the threshold for statistical significance.

2 Results

2.1 The varying expression levels of NUDT19 in tumor versus normal tissues

To examine the variations in NUDT19 expression between tumor and adjacent normal tissues, we conducted an in-depth analysis using various tools. mRNA levels were scrutinized *via* the TIMER2.0 database, revealing an up-regulation of NUDT19 expression in 17 tumor types, with down-

regulation observed solely in kidney renal clear cell carcinoma (KIRC) and pheochromocytoma and paraganglioma (PCPG) (Figure 1a). As the Timer 2.0 databases lacked matching normal tissues, we amalgamated data from TCGA with GTEx to assess NUDT19 expression across 34 cancers. Our analysis unveiled up-regulation of NUDT19 expression in 29 cancers, while down-regulation was evident in

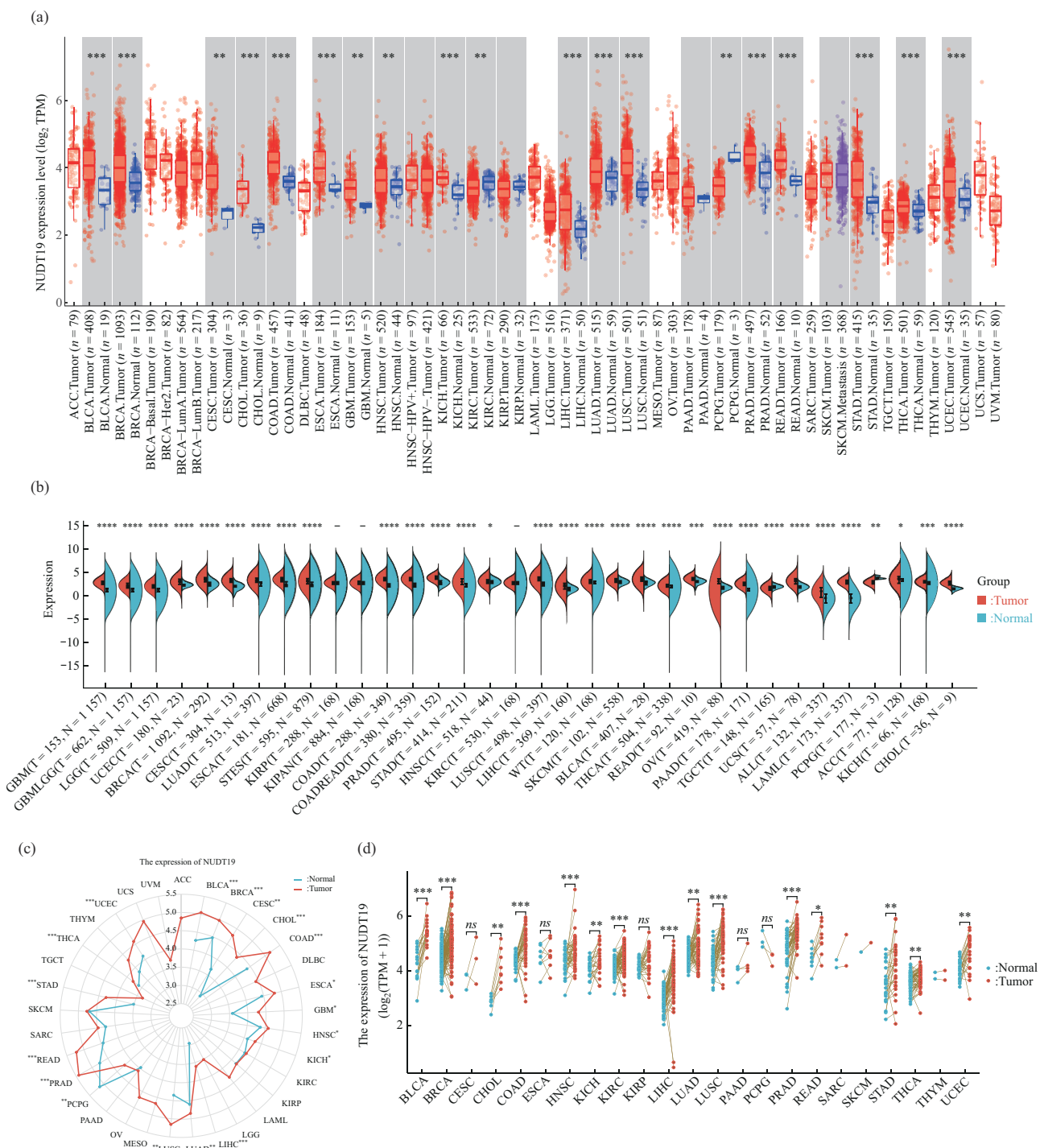


Fig. 1 Multiple tools were utilized to analyze the expression of NUDT19

(a) Box plots created using Timer 2.0 compared *NUDT19* mRNA expression in 33 different cancers, highlighting differences between tumor (red) and normal tissue (blue), with metastatic cutaneous melanoma (SKCM) highlighted in purple. (b) Utilizing Sangerbox 3.0, we analyzed discrepancies in *NUDT19* mRNA expression between tumor tissues sourced from the TCGA dataset and normal tissues from the GTEx dataset across various cancers, employing bean plots. T: tumor; N: normal. (c) A radar plot was generated to illustrate the pan-cancer expression pattern of *NUDT19*, displaying the dynamic variations in expression levels across various tumor types. (d) Paired tumor-normal box-line plots for 23 TCGA cancers. A significance threshold of $P < 0.05$ was deemed statistically significant. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, ns: no significance.

testicular germ cell tumors (TGCT) and PCPG compared to normal tissues (Figure 1b). Further analysis using radargrams demonstrated up-regulation of NUDT19 expression in uterine corpus endometrial carcinoma (UCEC), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), cholangiocarcinoma (CHOL), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), glioblastoma multiforme (GBM), lung adenocarcinoma (LUAD), stomach adenocarcinoma (STAD), liver hepatocellular carcinoma (LIHC), thyroid carcinoma (THCA), lung squamous cell carcinoma (LUSC), and bladder urothelial carcinoma (BLCA), whereas down-regulation was observed in PCPG (Figure 1c). Examination through paired sample maps indicated that NUDT19 expression was upregulated in tumor tissues of the majority of patients with BRCA, BLCA, CHOL, HNSC, COAD, KICH, KIRC, LUAD, LUSC, LIHC, prostate adenocarcinoma (PRAD), STAD, THCA, rectum adenocarcinoma (READ), and UCEC cancers (Figure 1d).

2.2 The prognostic value of NUDT19

To explore the prognostic relevance of NUDT19 expression across various cancers, we conducted analyses on OS, DSS, DFI, and PFI survival metrics. Our findings indicate that NUDT19 overexpression correlates with unfavorable OS in brain lower grade glioma (LGG), acute myeloid leukemia (LAML), acute lymphoblastic leukemia (ALL), BRCA, GBM, LAML, LIHC, *etc.* (Figure 2a). Additionally, elevated NUDT19 expression is associated with adverse DSS outcomes in GBMLGG, LGG, and GBM (Figure 2b). However, regarding DFI, no statistically significant correlation was found between NUDT19 expression and either favorable or unfavorable outcomes (Figure 2c). High NUDT19 expression is negatively linked with PFI in LGG, GBMLGG, and uveal melanoma (UVM) (Figure 2d).

2.3 Correlation of NUDT19 with clinicopathologic staging and its diagnostic value

We investigated the expression of NUDT19 across various pathological stages and observed significant differences in BRCA, BLCA, COAD, CHOL, LIHC, HNSC, LUAD, and STAD, compared

to normal conditions (Figure 3a). To evaluate the influence of gene expression on diagnostic accuracy, we conducted an analysis of the TCGA dataset to examine the ROC curves of NUDT19 across pan-cancer samples. Visualization of these curves revealed both strong diagnostic potential (*AUC* exceeded 0.9) and moderate diagnostic potential (*AUC* ranged between 0.7 and 0.9) associated with NUDT19 expression across a range of cancers. Notably, the *AUC* for CHOL was 1.0 (Figure 3b–m).

2.4 Association between NUDT19 expression and key tumor biomarkers

TMB, MATH, MSI, and NEO are pivotal biomarkers utilized for prognostic assessment, treatment selection, and immunotherapy in cancer. Employing Sanger Box 3.0, we evaluated the correlation between NUDT19 expression and these biomarkers. In our analysis, a noteworthy correlation emerged between NUDT19 expression and TMB across six tumors. Specifically, it displayed a significant positive correlation in 5 tumors, namely LUAD, LAML, BRCA, STAD, and stomach and esophageal carcinoma (STES), while demonstrating a significant negative correlation in one tumor, uterine carcinosarcoma (UCS) (Figure 4a). Regarding MATH, we observed significant correlation with NUDT19 expression in 11 tumors (Figure 4b). Upon deeper analysis, a strong correlation between NUDT19 expression and MSI was observed in 14 different types of tumors (Figure 4c). Lastly, the relationship between NUDT19 expression and NEO was investigated, revealing significant correlations in 4 types of tumors. Specifically, LUAD and UCEC exhibited a positive correlation, while COAD and colon adenocarcinoma/rectum adenocarcinoma esophageal carcinoma (COADREAD) displayed a significant negative correlation (Figure 4d).

2.5 Correlation of NUDT19 expression with immune-related genes

Firstly, we examined the relationship between NUDT19 expression and several gene categories, including chemokines, receptors, MHC molecules, immunoinhibitors, and immunostimulators. Our analysis unveiled a noteworthy correlation between NUDT19 expression and these genes across cancer types such as UVM, ovarian serous

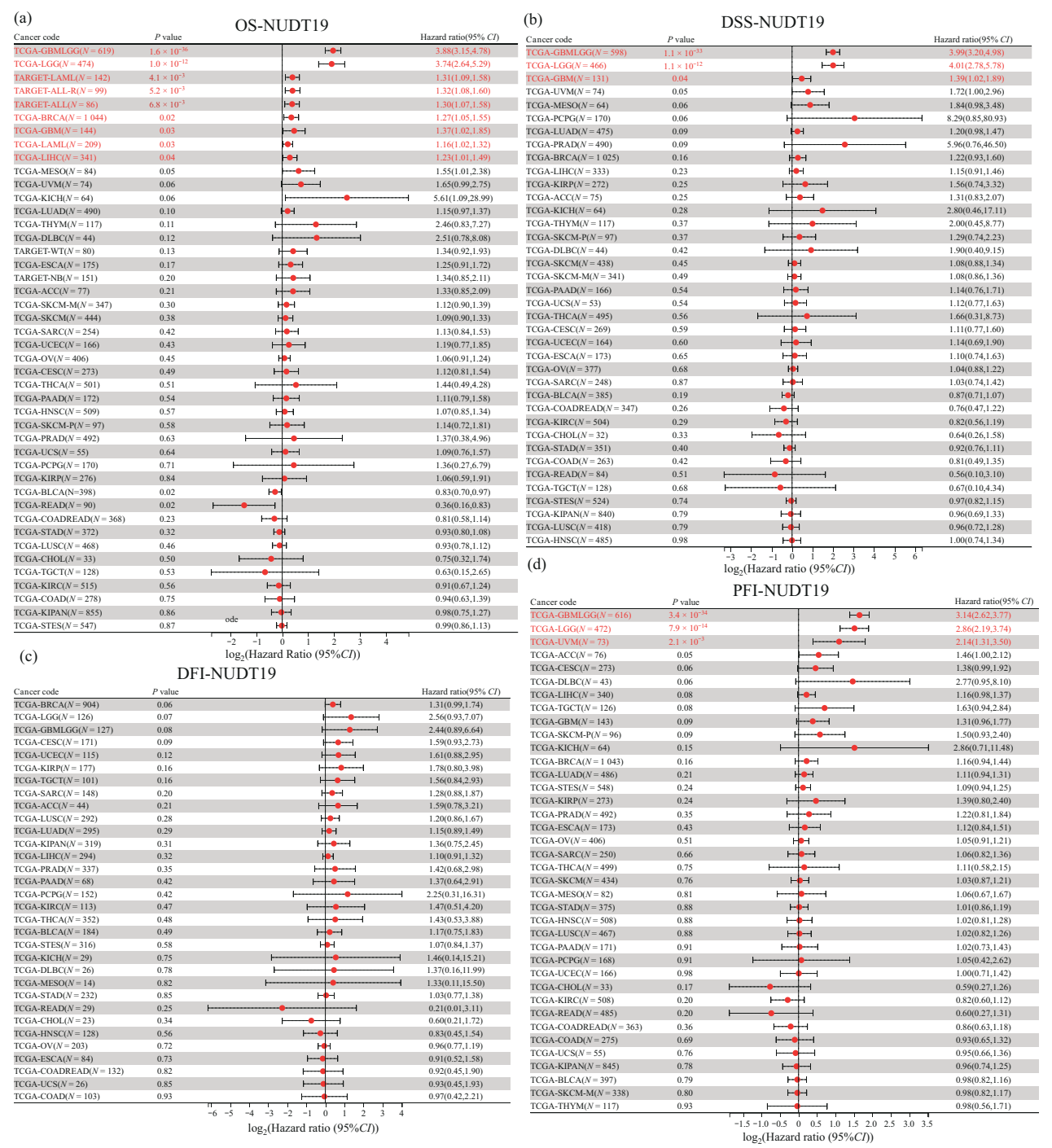


Fig. 2 The impact of NUDT19 expression on prognosis

NUDT19 expression and its association with OS (a), DSS (b), DFI (c), and PFI (d). A significance threshold of $P<0.05$ was deemed statistically significant.

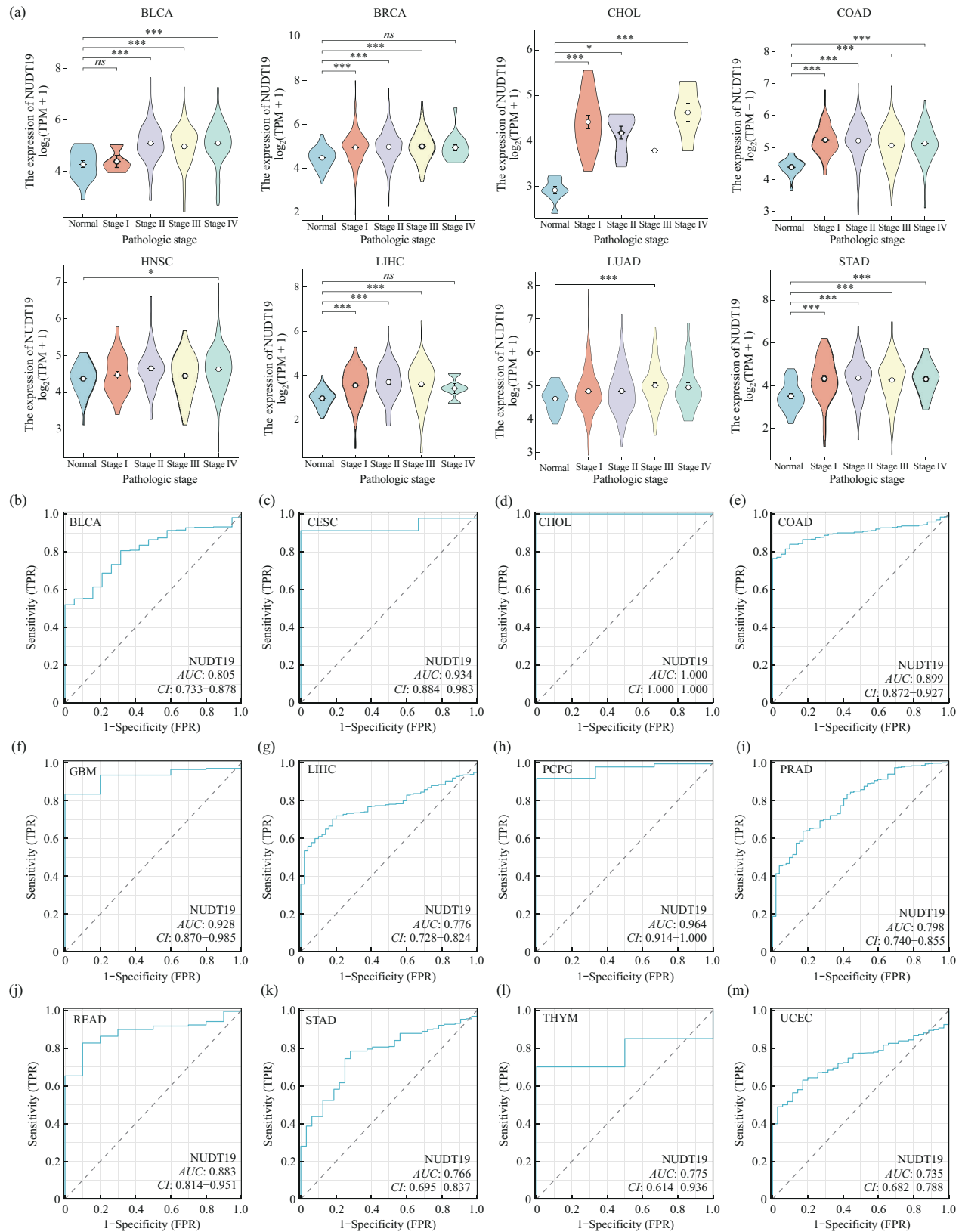


Fig. 3 Staging and diagnostic analysis of NUDT19

(a) Sangerbox3.0 analysis was utilized to explore the clinical relevance of NUDT19 across various pathological stages in pan-cancer. (b-m) ROC curves were constructed to evaluate the diagnostic effectiveness of NUDT19 in pan-cancer, with significance attributed to an *AUC* surpassing 0.7. **P* < 0.05, ****P* < 0.001, ns: no significance.

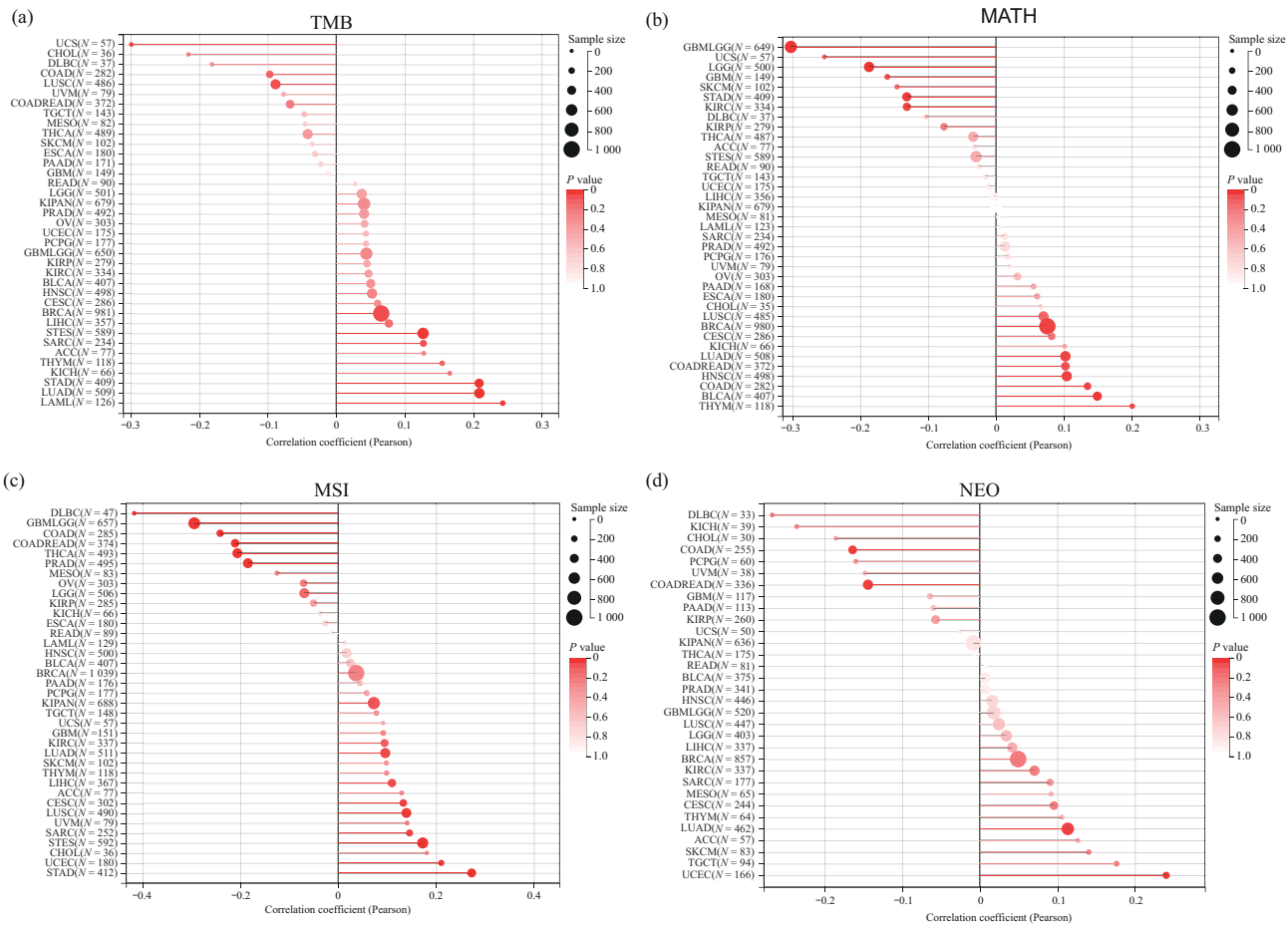


Fig. 4 Exploring the association between NUDT19 expression and biomarkers across diverse cancer types
(a-d) Bar charts illustrate the connection between NUDT19 expression and TMB (a), MATH (b), MSI (c) and NEO (d) levels. A significance threshold of $P<0.05$ was deemed statistically significant.

cystadenocarcinoma (OV), LGG, thymoma (THYM), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), and TGCT (Figure 5). Next, we investigated the relationship between NUDT19 expression and genes involved in inhibition and stimulation. Our findings uncovered a connection between NUDT19 expression and various genes across different cancer types (Figure 6).

2.6 The infiltration of immune cells is associated with NUDT19 expression

Immune cells infiltrating the tumor microenvironment (TME) are crucial in cancer development and progression, with a substantial impact on the clinical prognosis of cancer patients. To explore the connection between NUDT19 and immune-infiltrating cells across different cancers, we evaluated the correlation between NUDT19 expression and immune cell infiltration with Sanger

Box 3.0. The findings indicated that NUDT19 exhibited significant associations with all 6 subtypes of immune cells in LGG, KIRC, pan-kidney cohort (KICH+KIRC+KIRP) (KIPAN) and GBMLGG (Figure 7a). Subsequently, we evaluated the correlation between NUDT19 and immune-infiltrating cells using two algorithms: QUANTISEQ and xCELL. Our analysis unveiled a noteworthy association between NUDT19 expression and a wide range of immune cells (Figure 7b, c).

2.7 Mutations in NUDT19 and the correlation between NUDT19 and epigenetic factors

Given the potential association of copy number variation (CNV) with cancer development and progression, we examined the correlation between NUDT19 expression and CNV. Our analysis revealed significant differences in NUDT19 expression among groups of neutral, loss, and gain in CESC, LUAD,

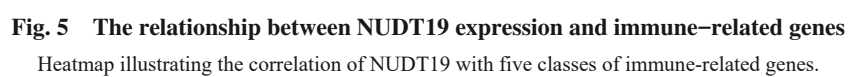
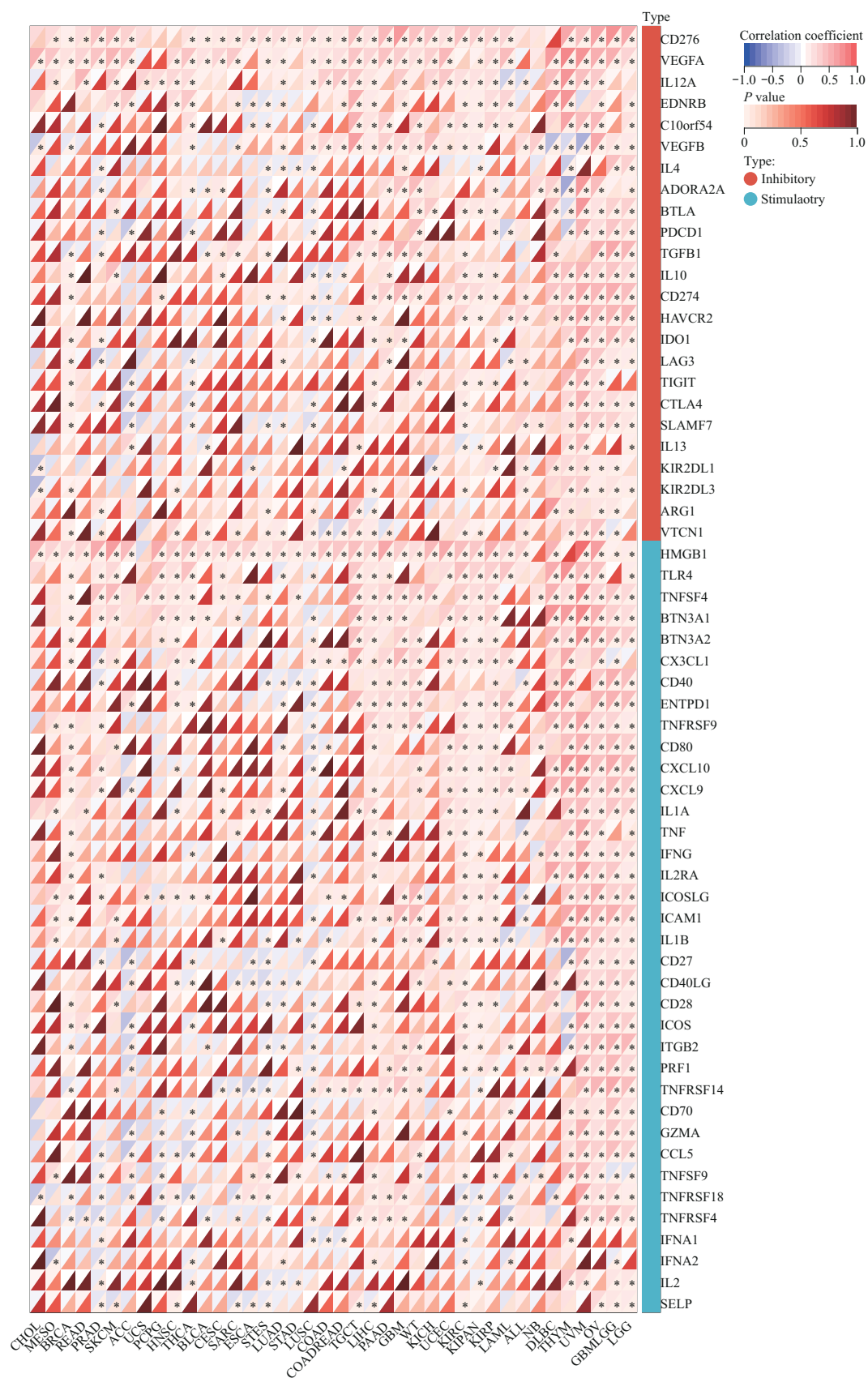


Fig. 5 The relationship between NUDT19 expression and immune-related genes
Heatmap illustrating the correlation of NUDT19 with five classes of immune-related genes.



A heatmap showing the correlation between NUDT19 and inhibitory as well as stimulatory genes across various cancers.

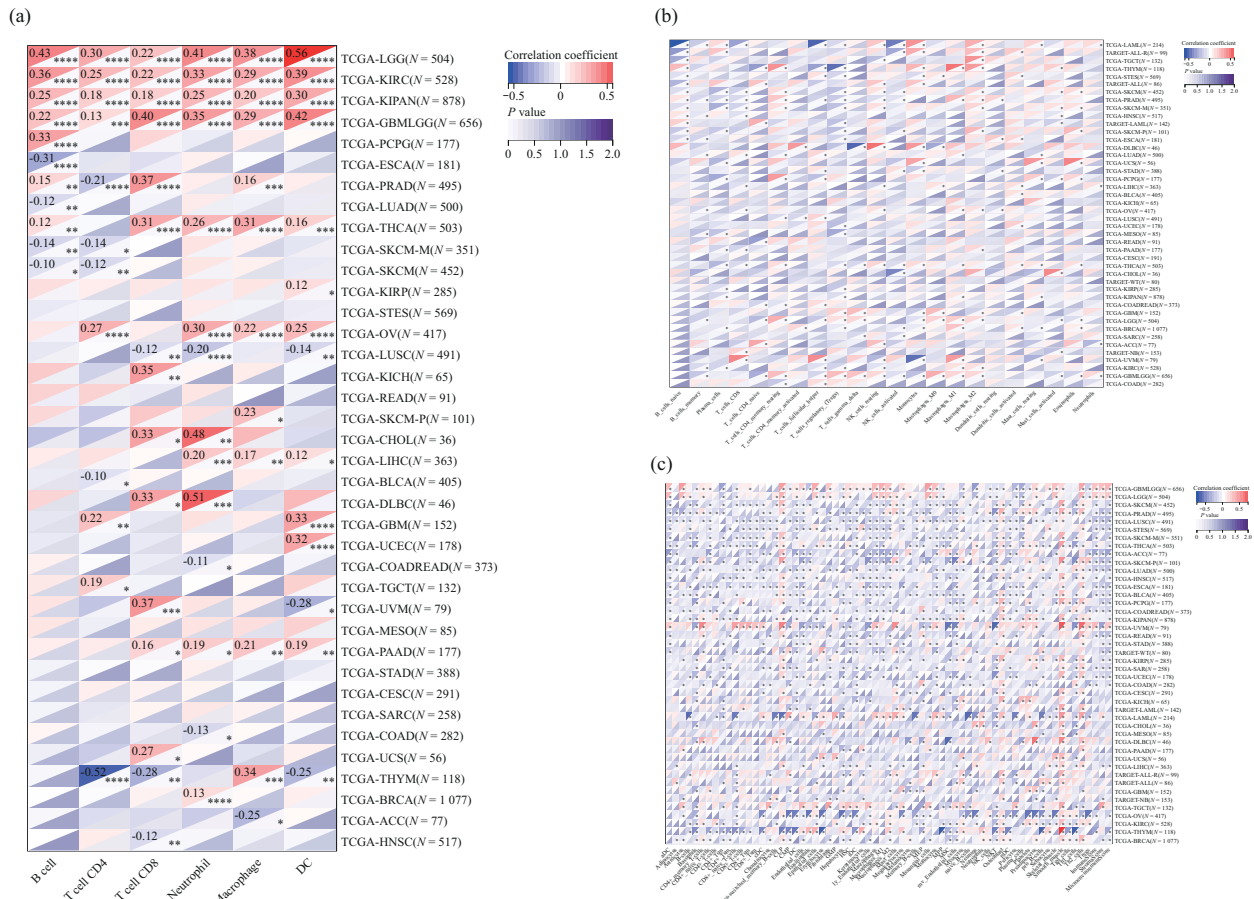


Fig. 7 Correlation of NUDT19 expression with immune-infiltrating cells utilizing various algorithms

(a) Timer, (b) QUANTISEQ, (c) xCELL. A significance threshold of $P < 0.05$ was deemed statistically significant. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

Esophageal carcinoma (ESCA), BRCA, sarcoma (SARC), STES, STAD, prostate adenocarcinoma (PRAD), UCEC, LUSC, HNSC, pancreatic adenocarcinoma (PAAD), OV, UCS, and BLCA (Figure 8a). To comprehensively explore the mutation profile of NUDT19, we conducted an extensive analysis of its mutation landscape across various tumors. Our findings revealed that NUDT19 exhibits missense mutations, frame shift insertions, and nonsense mutations, with missense mutations being the predominant alteration. Additionally, our investigation demonstrated that in cancer types including LIHC, KIRC, UCEC, KIPAN, LUAD, CESC, LGG, and GBM, only a single mutation site in NUDT19 is observed. In contrast, cancer types such as BLCA, OV, LUSC, HNSC, STAD, STES, COADREAD, COAD, and GBMLGG display multiple mutation sites within NUDT19 (Figure 8b). The intricate interplay between epigenetic

mechanisms and pivotal processes such as tumorigenesis, metastasis, and prognosis underscore their significance in cancer biology. To delve deeper into this relationship, we examined the correlation between NUDT19 and three DNA methylation transferase enzymes utilizing the Timer 2.0 database. Our analysis revealed a positive association between the expression levels of NUDT19 and the DNA methyltransferases DNMT1, DNMT3A, and DNMT3B in multiple cancer types (Figure 8c). Subsequently, we investigated the association between NUDT19 and three principal classes of RNA modification-related molecules, namely m1A, m5C, and m6A. Our analysis unveiled a positive correlation between NUDT19 and the majority of RNA-regulated genes across various cancer types (Figure 8d).

2.8 Functional enrichment analysis of NUDT19

To assess the functional role of NUDT19, we employed the STRING databases to identify 10 genes

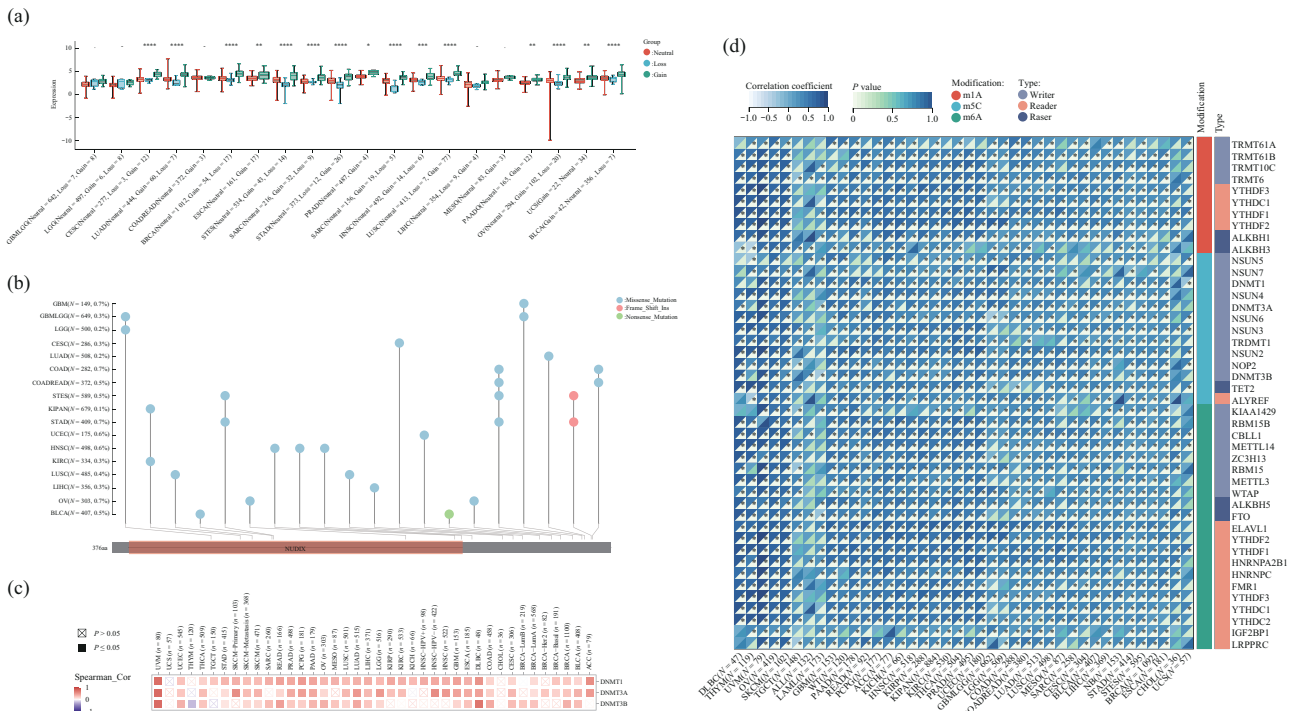


Fig. 8 Mutations in NUDT19 and the correlation between NUDT19 and epigenetic factors

(a) The relationship between NUDT19 expression and CNV was analyzed. (b) Genetic alteration characteristics of NUDT19 were assessed using the cBioPortal tool. (c) The correlation between NUDT19 expression and methyltransferases across pan-cancer was obtained from the Tisler 2.0 platform. (d) The association between NUDT19 expression and RNA modification-related genes was examined across 40 cancer types. A significance threshold of $P<0.05$ was deemed statistically significant. * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$.

interacting with NUDT19 (Figure 9a). Subsequently, employing the cytohubba plugin in Cytoscape, we screened the top 5 core genes in the PPI network and identified NUDT19, NUDT17, SCP2, TYSND1, and HSD17B4 as the core genes (Figure 9b). Following this, we conducted a comprehensive GO-KEGG enrichment analysis involving these 11 genes. The GO analysis identified biological process (BP) terms related to fatty acid catabolism, nucleotide catabolism, monocarboxylic acid catabolism, and nucleoside phosphate catabolism. Corresponding cellular component (CC) terms were associated with the microbody, peroxisome, microbody lumen, and peroxisomal matrix. Furthermore, the identified genes demonstrated molecular function (MF) involvement, including nucleotide diphosphatase activity, magnesium ion binding, cholesterol binding, and sterol binding (Figure 9c). Additionally, KEGG enrichment analysis highlighted the significant association of these genes with key pathways such as peroxisome, biosynthesis of unsaturated fatty acids, primary bile acid biosynthesis, and fatty acid metabolism (Figure 9d).

2.9 Single-cell analysis elucidates the distribution of NUDT19 across distinct cell types

To further investigate the cellular expression characteristics of NUDT19 in various cancers and to clarify its expression across different cell types and its pan-cancer conservation, this study utilized the scCancerExplorer platform to conduct single-cell analysis of BLCA, COAD, GBM, LIHC, PAAD, and cutaneous melanoma (SKCM). The selection of these cancers was based on their significant correlation with NUDT19 expression and key clinical indicators, such as prognosis, stage, and immune infiltration. Additionally, these cancers exhibit distinct immune microenvironment complexities and tumor heterogeneity—melanoma being highly immunogenic with a dynamic immune landscape, and pancreatic cancer characterized by high heterogeneity and immune suppression. This selection allows us to explore NUDT19’s functions at the single-cell level across diverse contexts.

First, we performed clustering on the single-cell data using the UMAP method to identify different cell

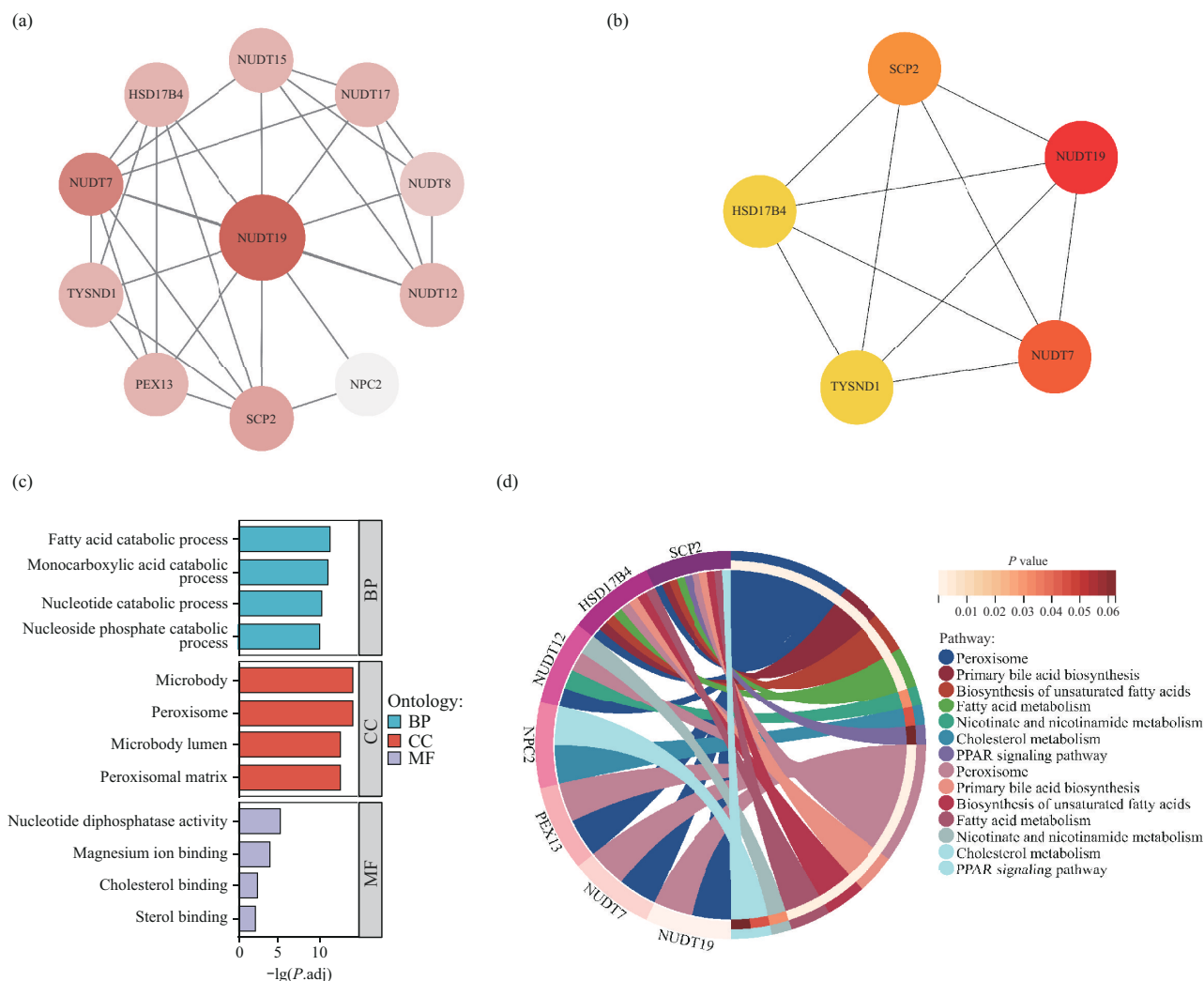


Fig. 9 Functional enrichment analysis of NUDT19

(a) A PPI network for NUDT19 was generated using the STRING web. (b) The core genes of the PPI network were identified using Cytohubba's MCC algorithm. (c) GO analysis of PPI network. (d) KEGG pathway analysis.

types. Next, we analyzed the expression levels of *NUDT19* gene in each cell cluster, visualizing the results using UMAP plots and violin plots. The results revealed cell-type-specific expression patterns of *NUDT19* across different cancers.

In BLCA, UMAP clustering divided the cells into types such as CD4T_conv, CD8T_typical, NK_cell, B_cell, and Mono/Macro. The UMAP plot, with a color gradient (blue for low expression, red for high expression), showed higher expression of *NUDT19* in certain cell subgroups. Quantitative analysis with the violin plot indicated significant expression differences of *NUDT19* in CD4T_conv, CD8T_typical, and other cell populations, particularly in the CD8T_typical immune cell subset (Figure 10a).

In COAD, after UMAP clustering, *NUDT19* was found to be highly expressed in cells labeled as Cancer_cell (Figure 10b). In GBM, UMAP clustering and expression analysis revealed significant *NUDT19* expression in the Cancer (neoplastic) and myeloid cell populations (Figure 10c). The single-cell analysis of LIHC showed prominent *NUDT19* expression in both Cancer_cells and T/NK cell clusters (Figure 10d). In PAAD, *NUDT19* exhibited higher expression in endothelial cells, lymphocytes, and certain tumor cell subpopulations (Figure 10e). Finally, in SKCM, *NUDT19* expression was notably high in CD8T_typical and CD8T_exhausted cell populations (Figure 10f).

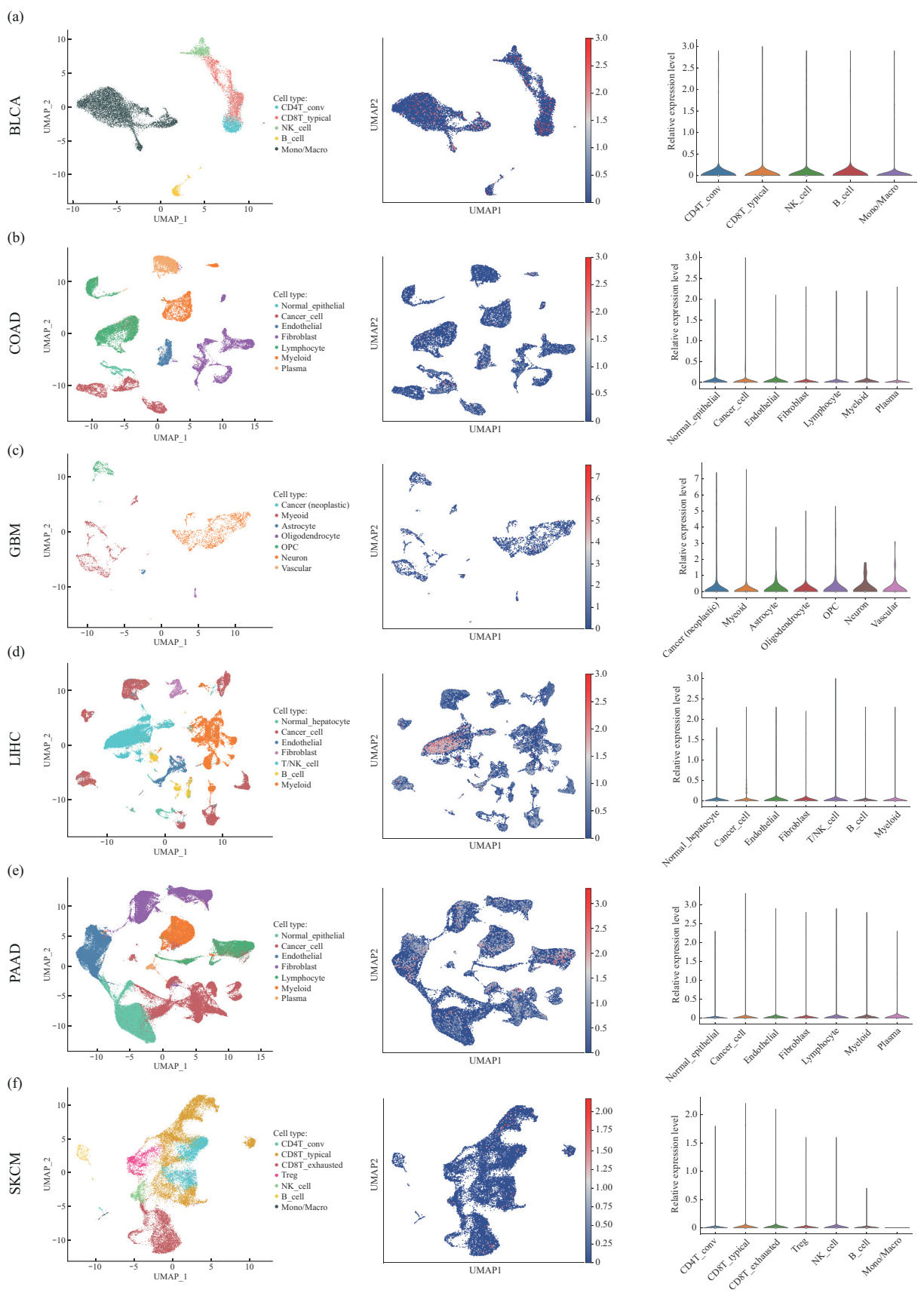


Fig. 10 Single-cell analysis of NUDT19 expression in various cancers was conducted using the scCancerExplorer platform (a) BLCA. (b) COAD. (c) GBM. (d) LIHC. (e) PAAD. (f) SKCM. Each figure consists of three parts: the left panel displays the UMAP clustering of cell types, the middle panel shows the expression of NUDT19 (with blue indicating low expression and red indicating high expression), and the right panel presents a violin plot illustrating the expression levels across different cell groups.

2.10 qRT-PCR experiment further confirms the bioinformatics findings

To authenticate the bioinformatics findings, we

confirmed mRNA expression in numerous cell lines, demonstrating upregulation of *NUDT19* mRNA in tumor cells such as T24, SW1116, HepG2, Calu-3, DU145, SGC-7901, HL-60, THP-1 (Figure 11a-h).

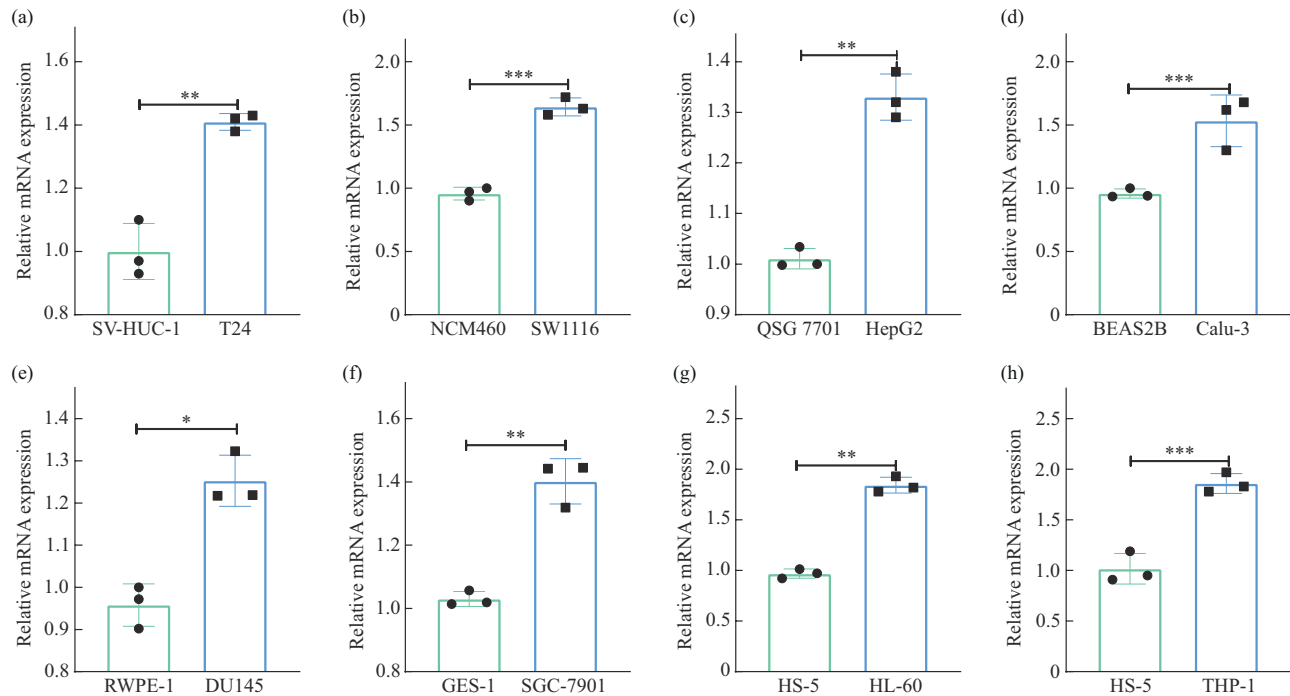


Fig. 11 *NUDT19* mRNA expression in tumor and corresponding normal cell lines

(a) SV-HUC-1 and T24 cells. (b) NCM460 and SW1116 cells. (c) QSG 7701 and HepG2 cells. (d) BEAS2B and Calu-3 cells. (e) RWPE-1 and DU145 cells. (f) GES-1 and SGC-7901 cells. (g) HS-5 and HL-60 cells. (h) HS-5 and THP-1 cells. A significance threshold of $P < 0.05$ was deemed statistically significant. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

2.11 Gene knockdown and overexpression of *NUDT19*

To explore the potential role of *NUDT19* in leukemia, we employed gene overexpression and knockdown strategies to manipulate *NUDT19* expression in HL-60 and THP-1 cell lines. qRT-PCR analysis confirmed a significant reduction in *NUDT19* mRNA levels after knockdown, while overexpression resulted in a substantial increase in *NUDT19* mRNA levels (Figure 12a, c). To verify the efficiency of these genetic manipulations, we performed Western blot analysis to assess *NUDT19* protein levels. The results demonstrated a significant reduction in *NUDT19* protein levels in knockdown cells and a marked increase in overexpressing cells, further validating the success of the gene modulation (Figure 12b, d).

2.12 Effects of *NUDT19* on cell proliferation and apoptosis

To explore the impact of *NUDT19* on leukemia cell proliferation, we performed CCK-8 assays to assess cell proliferation in HL-60 and THP-1 cells following *NUDT19* knockdown and overexpression. In HL-60 cells, *NUDT19* knockdown significantly reduced cell proliferation, whereas overexpression of *NUDT19* markedly enhanced proliferation. To verify the reliability of these findings, we conducted the experiment again in THP-1 cells and observed consistent results (Figure 13a, c). We also assessed the expression of the cell proliferation marker proliferating cell nuclear antigen (PCNA) via Western blot, which showed a significant decrease in PCNA levels after *NUDT19* knockdown and a marked

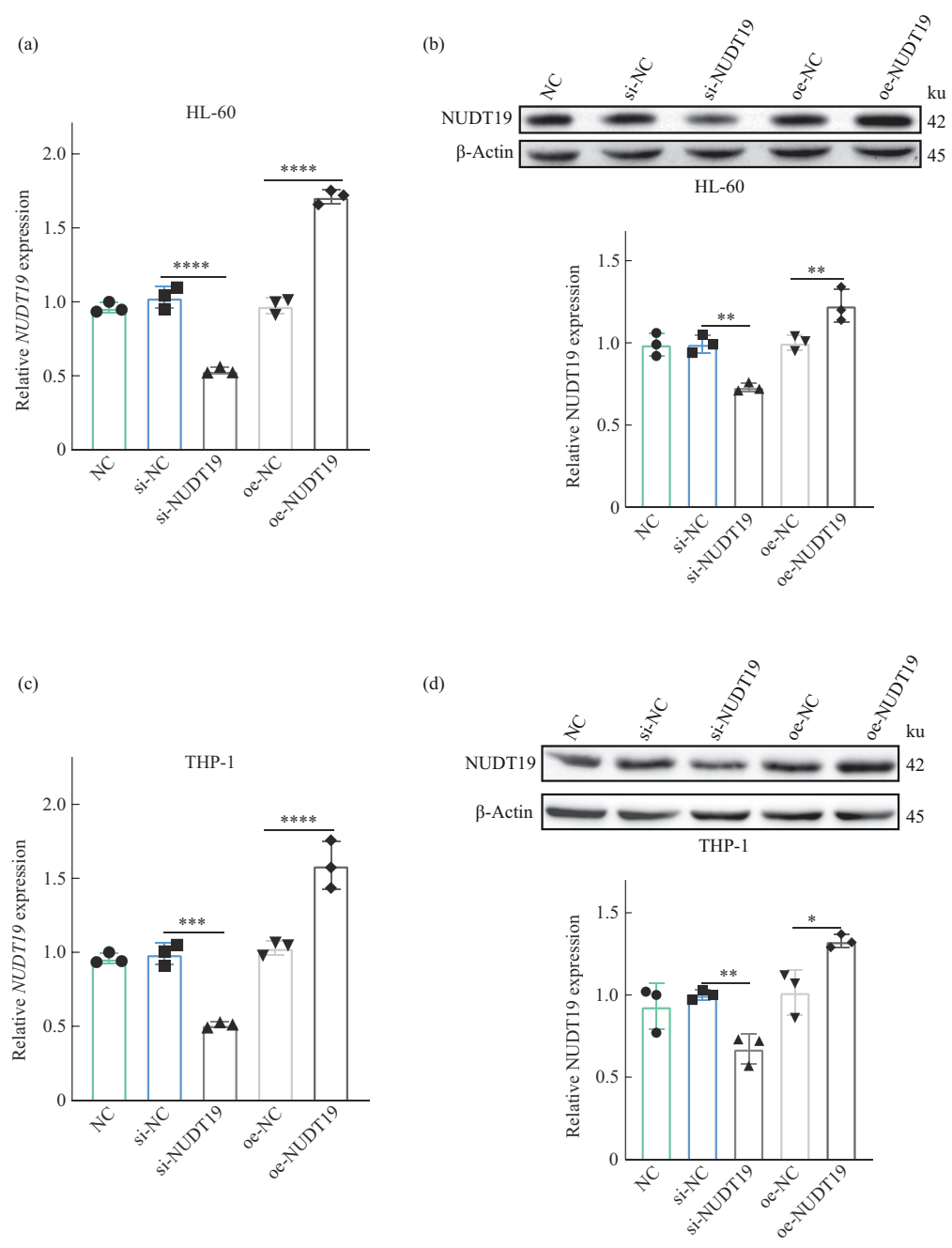


Fig. 12 Gene knockdown and overexpression of NUDT19 in HL-60 and THP-1 cell lines

(a, c) qRT-PCR analysis showing *NUDT19* mRNA expression levels in HL-60 and THP-1 cells following gene knockdown and overexpression. (b, d) Western blot analysis confirming the protein levels of NUDT19 in both cell lines after knockdown and overexpression. Statistical significance was determined using Student's *t*-test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

increase in NUDT19-overexpressing cells (Figure 13b, d).

Additionally, we investigated the effect of NUDT19 on apoptosis. Analysis of apoptosis-related proteins revealed that in HL-60 cells with NUDT19 knockdown, the expression of Caspase-3 and Bax elevated, whereas Bcl-2 expression was reduced. In

contrast, in NUDT19-overexpressing HL-60 cells, levels of Caspase-3 and Bax were reduced, while Bcl-2 expression increased. Similar findings were observed in THP-1 cells (Figure 13e, f).

2.13 Effects of NUDT19 on cell invasion

To further investigate the functional impact of NUDT19 on leukemia cells, we assessed cell invasion

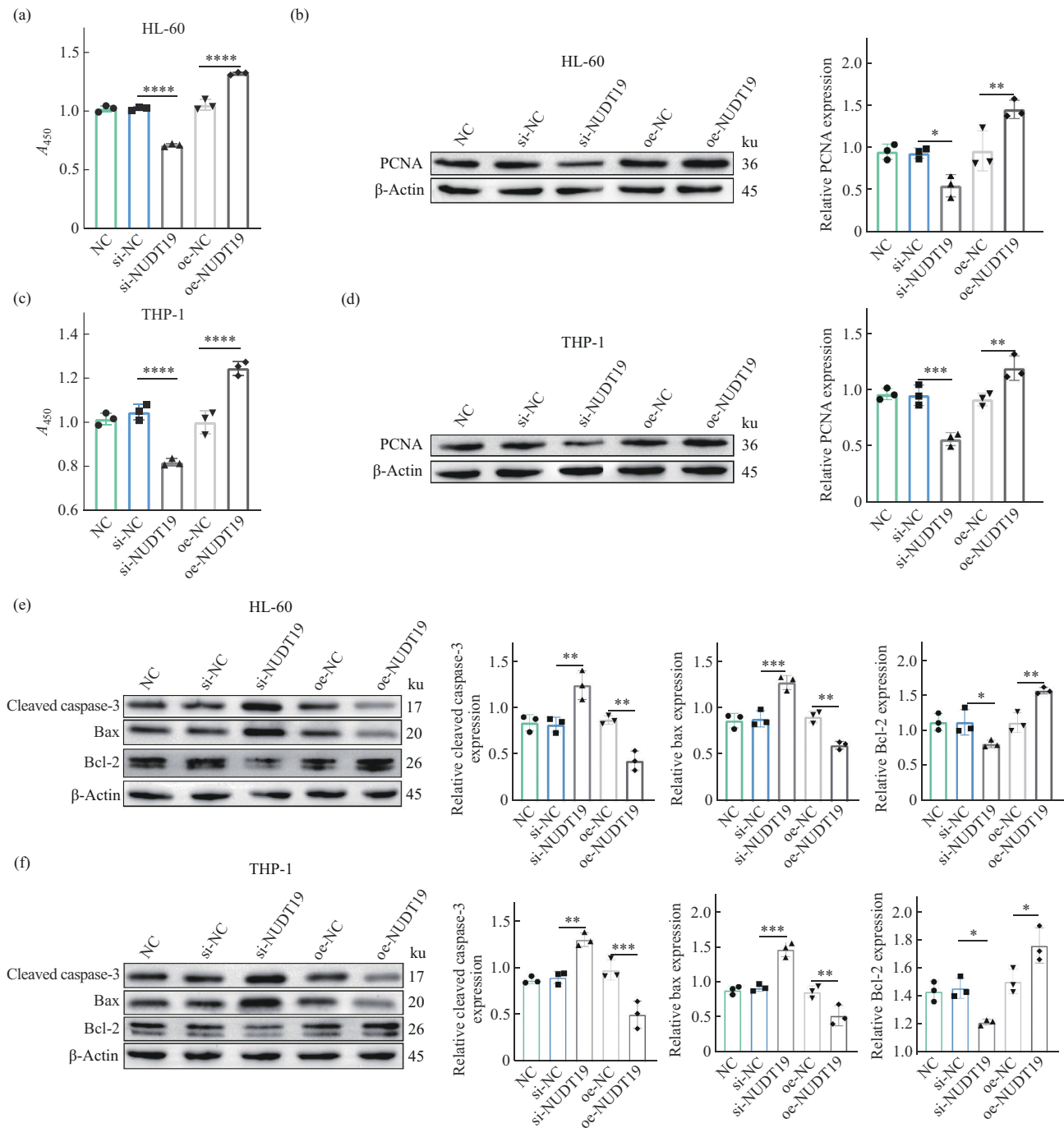


Fig. 13 Effects of NUDT19 on leukemia cell proliferation and apoptosis

(a, c) CCK-8 assays were performed to assess the effect of NUDT19 knockdown and overexpression on cell proliferation. (b, d) Western blot analysis of proliferation markers after NUDT19 knockdown and overexpression. (e, f) Western blot analysis of apoptosis-related markers following NUDT19 modulation. Statistical significance was determined using Student's *t*-test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

using transwell assays following NUDT19 knockdown and overexpression. The results indicated that NUDT19 knockdown significantly impaired cell invasion in both HL-60 and THP-1 cell lines, whereas NUDT19 overexpression promoted cell invasion (Figure 14a, c). In order to investigate the molecular mechanisms driving these phenotypic alterations, we

assessed the expression of proteins associated with cell invasion and migration through Western blot analysis. The findings showed that after silencing NUDT19, the levels of Vimentin, N-cadherin, MMP-2, and MMP-9 were substantially reduced, while their expression was significantly elevated in cells overexpressing NUDT19 (Figure 14b, d).

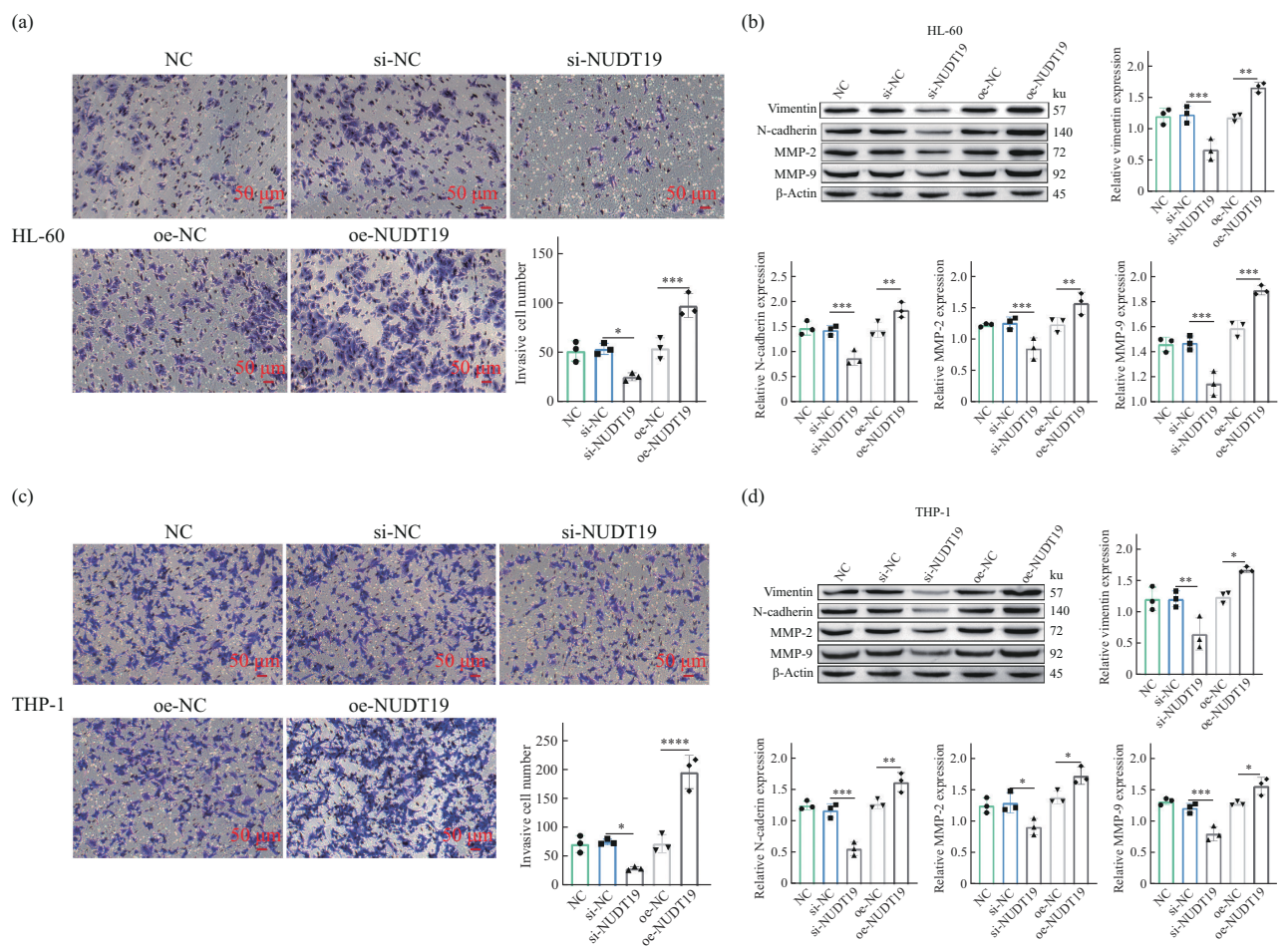


Fig. 14 The impact of NUDT19 on leukemia cell invasion

(a, c) Transwell invasion assays demonstrated that NUDT19 knockdown significantly reduces cell invasion, while NUDT19 overexpression increases invasion capacity. (b, d) Western blot analysis reveals that NUDT19 knockdown significantly decreases the expression of invasion-related proteins, while their expression is markedly increased in NUDT19-overexpressing cells. Statistical differences were assessed by Student's *t*-test. **P*<0.05, ***P*<0.01, ****P*<0.001, *****P*<0.000 1.

3 Discussion

Cancer ranks among the foremost causes of mortality on a global scale. Recently, the study of cancer biomarkers has attracted extensive attention from researchers^[22-24]. In our study, we identified NUDT19 as a critical and previously underexplored biomarker in pan-cancer. Specifically, NUDT19 exhibits dysregulation in its expression across various cancers, which correlates with diagnosis, clinical staging, and poor prognosis. Furthermore, NUDT19 expression is strongly associated with immune-related tumor characteristics, including key tumor biomarkers, immune gene expression, and immune cell infiltration. The qRT-PCR experiments further validated the bioinformatics findings. Finally,

functional experiments demonstrated that silencing NUDT19 inhibited proliferation and invasion while promoting apoptosis in leukemia cell lines. In contrast, overexpression of NUDT19 enhanced cell proliferation and invasion, while reducing apoptosis in the same leukemia cell lines.

Our study identified dysregulated expression of NUDT19 across multiple cancer types, with upregulation observed in most tumors. This dysregulation was consistent across various platforms and datasets. Specifically, NUDT19 was found to be upregulated in cancers such as BLCA, BRCA, CHOL, COAD, HNSC, KICH, LIHC, LUAD, LUSC, PRAD, READ, STAD, THCA, and UCEC, with consistent results across multiple databases. However, discrepancies arose in some cases. For instance, Timer

2.0 showed downregulation in KIRC, while other platforms did not. Similarly, in ESCA, different tools (Timer 2.0, Sangerbox 3.0, and radar plots) suggested upregulation, but paired sample analysis yielded conflicting results.

These inconsistencies are likely due to differences in data sources and statistical methods. Timer 2.0 uses TCGA data without normal tissue controls for some cancers, while Sangerbox 3.0 integrates datasets from UCSC, including TCGA, TARGET, and GTEx (PANCAN, Sample Size=19 131, Number of Genes=60 499), offering broader coverage. Radar plots utilize TCGA RNA-seq data processed *via* STAR from 33 tumor types, with paired samples derived from the TCGA-ALL pan-cancer project. These differing data sources and sample populations led to fundamental differences in the underlying information used for NUDT19 expression analysis, contributing to variations in results across tools. Additionally, varying statistical methods, such as Wilcoxon tests in Timer 2.0 and Sangerbox 3.0, and the Mann-Whitney U test in radar plots, contributed to the discrepancies. Despite these differences across tools and cancer types, we minimized the limitations of individual tools or datasets through cross-validation, ensuring high reliability and comprehensiveness in our results. Overall, our findings highlight the potential significance of NUDT19 in tumorigenesis and progression.

Previous studies have shown that dysregulated expression of NUDT19 is closely associated with tumorigenesis, progression, and poor prognosis. For example, upregulation of NUDT19 has been shown to activate the mTORC1/P70S6K signaling pathway, promoting proliferation, migration, and EMT in hepatocellular carcinoma (HCC) [16]. Furthermore, NUDT19 has been found to be closely related to fatty acid metabolism [17] and may possess potential mRNA decapping enzyme activity [13]. Fatty acid metabolism plays a crucial role in the rapid growth and energy demands of cancer cells, which often need to regulate fatty acid metabolic pathways to maintain their proliferative and migratory capabilities [25]. mRNA decapping is an important step in gene expression regulation and can significantly impact tumor cell proliferation, migration, and survival. For instance, Nudt3, a Nudix protein with decapping activity, has been shown to play an important role in cell migration. In MCF-7 breast cancer cells, reduced

levels of Nudt3 protein enhance cell migration, accompanied by increased lamellipodia extension. Importantly, this phenotype can be restored by reintroducing wild-type Nudt3 protein, but not by the catalytically inactive variant, indicating that the decapping activity of Nudt3 is crucial for regulating cell migration [26]. Based on these findings, NUDT19, as a potential decapping enzyme, may play a significant role in tumor cells by regulating processes such as mRNA stability, fatty acid metabolism, and cell migration.

Biomarkers are key to tumor diagnosis, clinical staging and prognosis, and are important for improving cancer treatment outcomes [27]. Our findings indicated that elevated expression levels of NUDT19 were linked to unfavorable clinical prognosis, implying that NUDT19 might serve as a promising tumor marker and could impact tumor survival and recurrence. We also observed that NUDT19 expression was associated with tumor diagnosis and had good diagnostic potential in multiple cancer types. In particular, its *AUC* value of “1” in CHOL highlights its potential as a reliable diagnostic marker.

Immunotherapy targeting immune checkpoint inhibitors has demonstrated notable therapeutic effectiveness in treating a diverse range of malignant tumors. However, this approach has a clinical response rate of approximately 30% and is associated with side effects and drug resistance. TMB, MATH, MSI, and NEO are emerging predictive markers for assessing the therapeutic efficacy of immune checkpoint inhibitors [28-29]. Our study identified correlations between NUDT19 and these biomarkers across various tumors, implying that NUDT19 holds promise as a potential biomarker for immunotherapy. The presence of immune cells within the TME has emerged as a pivotal factor influencing tumor progression, growth, and the development of drug resistance. This intricate interplay significantly impacts the clinical prognosis of cancer patients. Moreover, immune cell compositions within the TME have been closely linked to the efficacy of immunotherapeutic interventions [30-31]. Our investigation revealed an association between NUDT19 and various immune cell infiltrations, shedding light on its potential role in tumor development and therapeutic approaches. These findings offer valuable insights that may inform prognostic assessments of tumors, therapeutic

decision-making, and the formulation of immunotherapy strategies.

Mutations and epigenetic modifications are important causes of abnormal gene expression^[32]. This investigation revealed a significant correlation between the CNV of *NUDT19* gene and its expression levels across diverse cancer types. This suggests that *NUDT19* gene may be regulated by CNV, and CNV may be an important mechanism leading to changes in *NUDT19* expression levels. Furthermore, the findings elucidated variations in the mutation status of *NUDT19* among distinct cancer categories. Some cancer types may be more inclined to specific types of *NUDT19* mutations, whereas other cancer types may exhibit a more diverse spectrum of mutations. Such differences may reflect the different dependencies of different cancer types on *NUDT19* function and may also provide important information for the design of therapeutic strategies for different cancer types. DNA methylation stands out as the prevalent form of epigenetic modification, serving as a crucial mechanism in governing genome functionalities^[33]. DNMT1, DNMT3A, DNMT3B are DNA methylation transferase enzymes that play an important role in oncogene methylation. Our study demonstrated that *NUDT19* correlates with the expression of three DNA methylation transferase enzymes in a variety of tumors, which may imply that *NUDT19* affects gene expression and cellular function by regulating DNA methylation levels. Modification of RNA is crucial in regulating gene expression, as well as in cell signaling and the occurrence of diseases^[34-36], our discovery of *NUDT19*'s association with genes involved in RNA modification suggests its potential involvement in regulating this process. This finding could offer valuable insights into the role of RNA modification in cellular function and the onset of diseases.

Although the pan-cancer analysis highlights the potential role of *NUDT19* in various cancers, our primary focus is on its function in leukemia, particularly in AML. Given the high heterogeneity, rapid relapse, and treatment resistance associated with AML, the functional role of *NUDT19* in this context is especially significant. In this study, we explored the potential of *NUDT19* as a biomarker for leukemia through bioinformatics analysis followed by experimental validation. Our findings suggest that *NUDT19* is crucial in regulating leukemia cell

proliferation, invasion, and apoptosis, underscoring its potential as both a prognostic marker and a therapeutic target. The modulation of *NUDT19* expression appears to have a profound impact on the biological behavior of leukemia cells, which could have therapeutic implications. Targeting *NUDT19* could potentially inhibit leukemia cell proliferation and invasion while promoting apoptosis, offering a novel approach for treatment. Notably, the pro-cancerous functions of *NUDT19* observed in leukemia (*e.g.*, promoting proliferation and inhibiting apoptosis) are highly consistent with its high expression and association with poor prognosis in pan-cancer analysis. The pan-cancer study also highlighted conserved mechanisms regulated by *NUDT19*, such as EMT and metabolic reprogramming, providing a theoretical framework for understanding its role in leukemia. Specifically, the *NUDT19*-dependent cell invasion observed in AML closely resembles the EMT activation mechanism mediated by *NUDT19* in liver cancer. These cross-cancer similarities suggest that *NUDT19* could be a promising therapeutic target. This discovery not only expands the functional profile of *NUDT19* but also offers new insights into immunotherapy for AML. Additionally, considering the association between *NUDT19* expression and immune-related features, further research is needed to explore how *NUDT19* could influence immune evasion in leukemia and other cancers.

In summary, our study reveals the dysregulation of *NUDT19* expression across various cancers and highlights its potential role in tumor immune regulation. Furthermore, it emphasizes the promising potential of *NUDT19* as a biomarker for prognosis, diagnosis, and immunotherapy, particularly in the context of leukemia.

4 Conclusion

This study illustrates the multifaceted functions of *NUDT19* across different types of cancer, with a particularly significant role in leukemia. *NUDT19* is not only linked to the initiation of tumors but may also contribute to cancer progression by regulating the immune microenvironment and epigenetic mechanisms. Our findings emphasize the potential of *NUDT19* as a therapeutic target, especially for targeted therapies in cancers like leukemia, offering promising clinical applications.

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NUDT19在泛癌类型中的多组学分析及其在白血病中的功能作用*

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摘要 **目的** 近期研究强调了核苷二磷酸连接部分X型基序19 (nucleoside diphosphate-linked moiety X motif 19, NUDT19) 在特定类型癌症的起始、进展和预后中的关键作用。然而, 它在不同癌症中的表达及作用仍未得到充分表征。本研究旨在通过多组学分析系统地探讨NUDT19在多种癌症类型中的表达模式、临床意义及免疫相关功能, 进一步揭示其在癌症中的潜在作用, 特别是在白血病中的功能和靶点价值。**方法** 为了实现上述目标, 本研究采用多种生物信息学方法评估NUDT19在肿瘤和正常组织中的表达模式、临床意义以及免疫相关功能。分析NUDT19的突变特征及其与表观遗传修饰的关系。使用单细胞分析工具SingleCellBase, 探讨NUDT19在肿瘤中不同细胞亚群中的分布。为了验证这些发现, 通过qRT-PCR实验测定了特定肿瘤细胞系中NUDT19的表达水平, 并通过建立急性髓系白血病 (AML) 细胞系 (HL-60 和 THP-1), 进行NUDT19敲低和过表达实验, 评估其对白血病细胞增殖、凋亡和侵袭的影响。**结果** 泛癌分析结果揭示了NUDT19在多种癌症类型中的表达失调, 且与不良预后、临床分期和诊断指标密切相关。此外, NUDT19与肿瘤生物标志物、免疫相关基因和免疫细胞浸润存在显著关联。突变分析显示, NUDT19的多个突变与表观遗传改变显著相关。单细胞分析进一步揭示了NUDT19在癌细胞中的表达异质性, 提示其在不同细胞亚群中可能发挥多样化功能。qRT-PCR实验验证了NUDT19在多种肿瘤细胞系中的显著上调。在AML细胞系中发现, NUDT19敲低导致细胞增殖和侵袭能力下降, 且细胞凋亡增加, 而NUDT19过表达则显著增强了细胞增殖和侵袭能力, 同时减少了细胞凋亡。**结论** NUDT19在多种癌症类型中发挥多样化作用, 尤其在白血病中的功能作用突出。NUDT19不仅与肿瘤的发生发展相关, 还可能通过调节免疫微环境和表观遗传机制影响癌症进程。本研究揭示了NUDT19作为潜在治疗靶点的价值, 尤其是对于白血病等恶性肿瘤的靶向治疗具有重要的临床应用前景。

关键词 NUDT19, 泛癌, 免疫治疗, 单细胞分析

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