

UBE2A as a prognostic indicator across human cancers: Insights from multi-omics and immune landscape analyses

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Abstract. Ubiquitin-conjugating enzyme E2A (UBE2A), a member of the ubiquitin-conjugating E2 enzyme family, has been implicated in tumor development; however, its role across human cancer types remains incompletely understood. The present study aimed to systematically characterize the expression pattern, prognostic importance and immune relevance of UBE2A in a pan-cancer context. Public datasets, including The Cancer Genome Atlas, Gene Expression Omnibus and Genotype-Tissue Expression, were integrated to evaluate UBE2A expression, clinical importance, molecular characteristics, immune associations and biological functions across cancer types. Single-cell RNA sequencing data were analyzed

to investigate the cellular distribution of UBE2A. Functional validation was performed through UBE2A knockdown in breast cancer cell lines. Results indicated that UBE2A was significantly upregulated in a number of cancer types and was associated with unfavorable overall and progression-free survival. UBE2A expression exhibited significant correlations with immune cell infiltration and immune checkpoint-associated genes across cancer types. Functional enrichment analyses indicated that UBE2A was primarily involved in cell cycle regulation and proliferative processes. Single-cell analysis revealed preferential UBE2A expression in proliferative T-cell populations. Furthermore, *in vitro* experiments demonstrated that UBE2A knockdown significantly suppressed breast cancer cell proliferation, migration and invasion. Overall, UBE2A was shown to be a promising prognostic biomarker associated with tumor progression, cell cycle activity and immune-associated characteristics across cancer types. Its preferential expression in proliferative T-cell populations and oncogenic role in breast cancer suggest that UBE2A may serve as a potential therapeutic target and a candidate biomarker for evaluating tumor prognosis and the tumor immune microenvironment.

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Abbreviations: UBE2A, ubiquitin conjugating enzyme E2A; TCGA, The Cancer Genome Atlas; GTEx, Genotype-Tissue Expression Project; ROC, receiver operating characteristic; AUC, area under the curve; OS, overall survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; RFS, relapse-free survival; GSEA, Gene Set Enrichment Analysis; KEGG, Kyoto Encyclopedia Of Genes And Genomes; GO, Gene Ontology; TMB, tumor mutational burden; MSI, microsatellite instability analysis; CCK-8; Cell Counting Kit-8; BLCA, bladder urothelial carcinoma; CESC, cervical squamous cell carcinoma; CHOL, cholangiocarcinoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head-neck squamous cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; STAD, stomach adenocarcinoma; gastric adenocarcinoma; THCA, thyroid carcinoma; COAD, colon adenocarcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; PRAD, prostate adenocarcinoma; STES, stomach and esophageal carcinoma; ESAD, esophageal adenocarcinoma; UVM, uveal melanoma; SARC, sarcoma; THYM, thymoma; TISCH2, Tumor Immune Single Cell Hub 2

Key words: ubiquitin-conjugating enzyme E2, pan-cancer, prognosis, immune infiltration, breast cancer, biomarker

Introduction

Cancer remains a leading cause of morbidity and mortality worldwide and continues to pose a notable burden on global health systems (1). Epidemiological projections have indicated that the incidence of cancer is expected to rise markedly in the coming decades, with ~35 million new cases annually by 2050 (1,2). A defining feature of malignant diseases is their pronounced heterogeneity, encompassing distinct molecular architectures, clinical trajectories and responses to therapy across cancer types and even among patients with the same diagnosis (3,4). Therapeutic strategies for cancer have evolved markedly, extending beyond traditional modalities such as surgery, chemotherapy and radiotherapy to include targeted agents and immune-based interventions, which have achieved durable benefits in selected patient populations (5,6). Despite this, treatment resistance, tumor plasticity and immune escape remain major obstacles that limit long-term efficacy and frequently result in disease relapse (7). Increasing evidence has suggested that these difficulties are associated with the dynamic interactions between tumor cells and the surrounding immune microenvironment, highlighting the urgent need to

identify novel molecular determinants that can inform more effective therapeutic strategies (8-10).

In recent years, pan-cancer analytical frameworks have emerged as important tools for elucidating shared and context-specific molecular features across numerous tumor types. By integrating large-scale genomic, transcriptomic and epigenomic datasets, pan-cancer approaches enable systematic comparisons that are not feasible within single-cancer studies, thereby facilitating the identification of conserved oncogenic programs as well as lineage-restricted alterations (11). Beyond nucleic acid-based analyses, contemporary pan-cancer investigations have begun to increasingly incorporate proteomic, metabolomic and immunological data, allowing for a more nuanced depiction of tumor biology and its regulatory networks (12-14). Such integrative strategies have contributed to the refinement of molecular classification systems and have supported a shift toward precision oncology paradigms that prioritize molecular characteristics over the tissue of origin (15).

Ubiquitin conjugating enzyme E2A (UBE2A), also known as RAD6A, is encoded on the Xq24 locus and functions as a core component of the ubiquitin-proteasome system (UPS). Through its interaction with specific E3 ligases, UBE2A participates in ubiquitin transfer reactions that are key in maintaining cellular homeostasis, including the regulation of DNA damage responses, cell cycle progression and protein turnover (16-18). Dysregulation of UPS-associated enzymes has been increasingly recognized as a contributor to malignant transformation and tumor progression (19,20). Accumulating studies have implicated aberrant UBE2A activity in a number of malignancies. For example, recurrent mutations in UBE2A have been reported in blast crisis chronic myeloid leukemia, where they disrupt myeloid differentiation and facilitate disease advancement (21). In hepatocellular carcinoma, UBE2A overexpression driven by the hsa_circ_0001394/miR-527 regulatory axis has been associated with enhanced tumor aggressiveness and adverse clinical outcomes (22). Despite these observations, the expression landscape, prognostic importance and biological functions of UBE2A across human cancer types have not been systematically investigated. In addition, its potential involvement in tumor immune regulation and the cellular contexts in which UBE2A is preferentially expressed remain largely unclear.

Therefore, the present study conducted a comprehensive pan-cancer analysis to characterize the expression landscape, prognostic importance and molecular features of UBE2A across human malignancies. Its associations with the tumor immune microenvironment were further explored through analyses of immune infiltration patterns, immune checkpoint-associated genes and immunoregulatory signatures. In addition, single-cell transcriptomic datasets were analyzed to investigate the cellular distribution of UBE2A and its potential functional states within the tumor microenvironment. Functional enrichment analyses and protein-protein interaction (PPI) network analyses were performed to elucidate the biological processes associated with UBE2A. Finally, the oncogenic role of UBE2A was experimentally validated in breast cancer cells. Collectively, the present study aimed to provide a comprehensive overview of UBE2A in cancer and offers insights into its potential roles in tumor progression

and tumor-immune interactions. The overall study design is illustrated in Fig. 1.

Materials and methods

Gene expression analysis. UBE2A expression across human cancer types was analyzed using RNA-sequencing (RNA-seq) data obtained from The Cancer Genome Atlas (TCGA; <https://portal.gdc.cancer.gov/>). Transcript per million (TPM)-format expression matrices processed using the STAR pipeline were downloaded and normalized by $\log_2(\text{TPM}+1)$ transformation. Differential expression analyses between tumor and normal tissues were performed in R software (version 4.2.1; Posit Software, PBC) using the Wilcoxon rank-sum test and data visualization was conducted using the 'ggplot2' package (version 3.4.4) (23). For tumor types lacking sufficient normal tissue controls in TCGA, the pan-cancer differential expression module of SangerBox (<http://sangerbox.com/>) was additionally used, which integrates TCGA and Genotype-Tissue Expression (GTEx; <https://www.gtexportal.org/home/>) datasets (24). To validate the expression pattern of UBE2A, two independent breast cancer cohorts [GSE29044 (25) and GSE65194 (26)] were downloaded from the Gene Expression Omnibus (GEO; <https://www.ncbi.nlm.nih.gov/geo/>) and differential expression analyses were performed between tumor and normal tissues using the same statistical methods. In addition, the associations between UBE2A expression and immune or molecular subtypes across cancers were explored using the Tumor-Immune System Interaction Database (<http://cis.hku.hk/TISIDB/>) (27).

Clinicopathological correlation analysis. To investigate the association between UBE2A expression and clinicopathological characteristics across cancers, normalized pan-cancer transcriptomic data (TCGA Pan-Cancer; $n=10,535$) were downloaded from the UCSC Xena database (<https://xenabrowser.net/>). UBE2A expression data were extracted from the dataset and samples derived from primary tumors were included for further analysis. Expression values were transformed using $\log_2(x + 0.001)$ normalization prior to statistical analysis. Differences in UBE2A expression among different clinicopathological stages, including T stage, N stage and pathological stage, were analyzed using R software. Unpaired Student's t-tests were used for pairwise comparisons, while one-way ANOVAs were performed for comparisons among multiple groups.

Diagnostic performance analysis. Diagnostic performance of UBE2A expression in distinguishing tumor tissues from normal tissues was evaluated using receiver operating characteristic (ROC) curve analysis. RNA-seq expression data in TPM format and corresponding clinical information were downloaded from TCGA. Gene expression values were transformed using $\log_2(\text{TPM} + 1)$ normalization prior to analysis. ROC analyses were performed in R software using the 'pROC' package (version 1.18.0) (28) and visualization was generated using the 'ggplot2' package (version 3.4.4) (23). Tumor samples were defined as the positive group, whereas normal tissues served as the reference group for binary classification analysis. The 'pROC' package automatically determined the direction

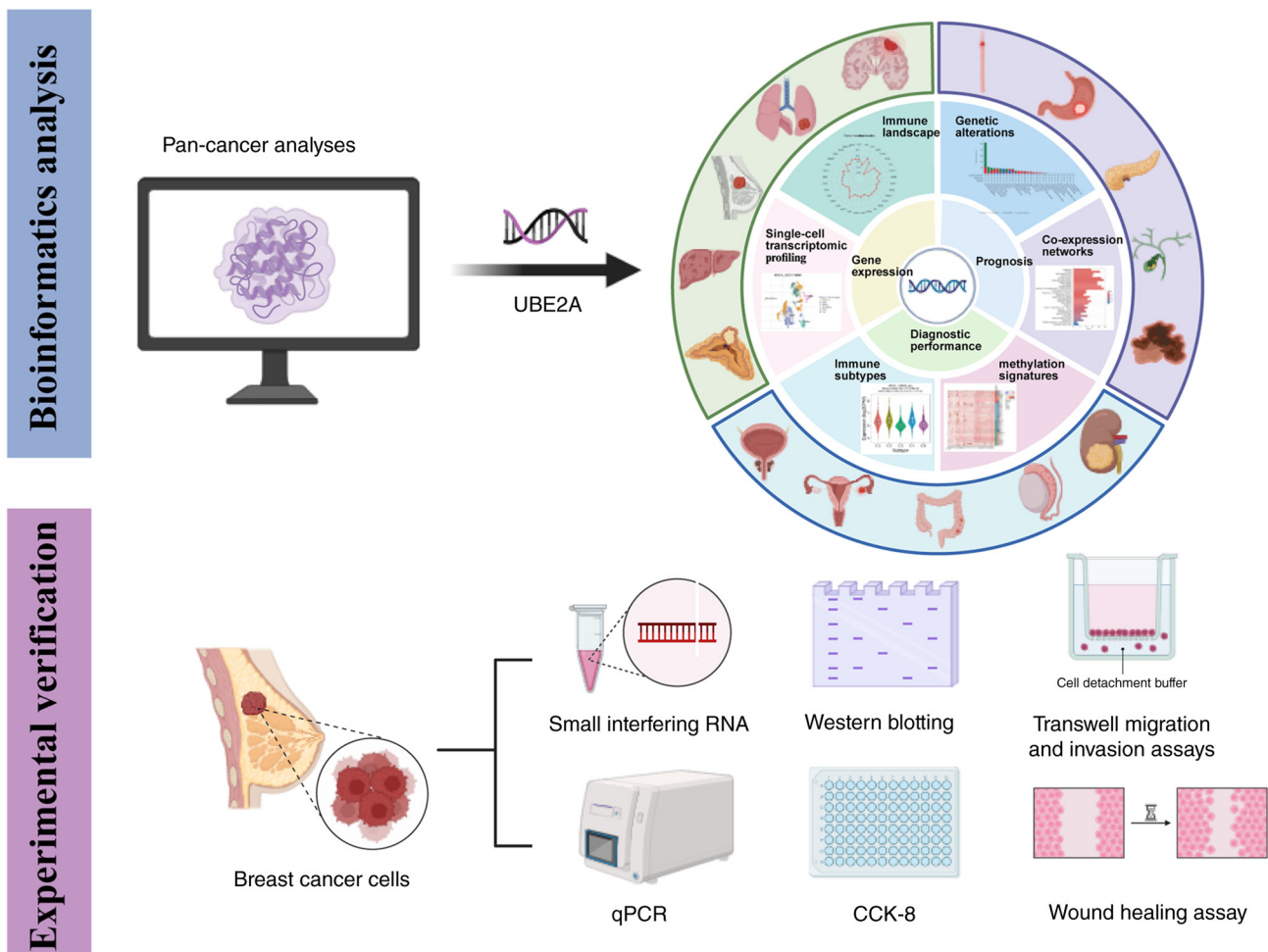


Figure 1. Study overview. An integrated pan-cancer analysis based on The Cancer Genome Atlas datasets was performed to systematically characterize the expression patterns, prognostic value, epigenetic regulation and immune relevance of UBE2A. *In vitro* functional assays in breast cancer cell lines further validated the oncogenic role of UBE2A in cancer progression. The graphical abstract was created using BioRender. UBE2A, ubiquitin conjugating enzyme E2A; qPCR, quantitative PCR; CCK-8; Cell Counting Kit-8.

of comparison to ensure an upward ROC curve orientation. The area under the ROC curve (AUC), sensitivity, specificity and optimal cut-off values were calculated to assess diagnostic efficacy. The optimal cut-off threshold was determined based on the maximum Youden index. An AUC value closer to 1.0 indicated superior discriminative performance. Pan-cancer analyses were performed across TCGA datasets and cancer types with significant diagnostic performance are presented in the results.

Survival prognosis analysis. Prognostic value of UBE2A was evaluated using the GEPIA2 (<http://gepia2.cancer-pku.cn/#analysis>) and Kaplan-Meier Plotter (<http://kmplot.com/analysis/>) databases. GEPIA2, which integrates transcriptomic and clinical data from TCGA, was used to assess the associations between UBE2A expression and overall survival (OS) as well as disease-free survival (DFS) using the log-rank test (29). Kaplan-Meier Plotter, which incorporates survival data from TCGA and GEO cohorts, was used to further validate the prognostic importance of UBE2A in breast cancer, including OS, distant metastasis-free survival (DMFS) and relapse-free survival (RFS). Patients were stratified into high- and low-expression groups

using the default cut-off settings of each platform. Hazard ratios (HRs), 95% CIs and log-rank P-values were used to evaluate prognostic importance (30).

Genetic alteration analysis. Genetic alteration data for UBE2A were obtained from the cBioPortal platform, which provides access to TCGA-based cancer genomics datasets (31). Alteration frequency, mutation type, mutation distribution and copy number variation of UBE2A were assessed across multiple cancer types. In addition, the associations between UBE2A genetic alterations and clinical outcomes were evaluated.

Co-expression analysis and gene set enrichment analysis (GSEA). Genes co-expressed with UBE2A were identified using the LinkedOmics database, which contains multi-omics data from TCGA cohorts (32). Pearson correlation analysis was performed to determine genes significantly associated with UBE2A expression. The top 500 positively and negatively correlated genes were subsequently subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses using the 'clusterProfiler' R package (version 4.14.6) (33-35). In addition, GSEA was performed in the TCGA-BRCA cohort by comparing samples with high and

low UBE2A expression (median cut-off). Genes were ranked according to differential expression and significantly enriched pathways were visualized using the 'enrichplot' package (version 1.26.6) (34).

PPI network analysis. A PPI network centered on UBE2A was constructed using the GeneMANIA platform (<http://genemania.org>) (36). Genes functionally associated with UBE2A were identified based on numerous evidence sources, including co-expression and physical interactions, to explore the potential molecular functions of UBE2A.

DNA methylation and RNA modification gene correlation analysis. Epigenetic modifications, including DNA methylation and RNA methylation, serve key roles in cancer development and progression (37,38). Promoter DNA methylation levels of UBE2A across 33 TCGA cancer types were evaluated using TCGA HumanMethylation450 BeadChip data accessed through the UALCAN platform (<http://ualcan.path.uab.edu>) (39). In addition, correlations between UBE2A expression and RNA modification-associated regulators, including genes involved in m6A, m5C and m1A modification pathways, were analyzed to explore potential epigenetic regulatory mechanisms.

Immune infiltration analysis. Immune cell infiltration levels were estimated using the Cell-type Identification by Estimating Relative Subsets of RNA Transcripts algorithm (40) based on TCGA transcriptomic data. The relative proportions of 22 immune cell subsets were quantified and Spearman's correlation analysis was performed to evaluate the associations between UBE2A expression and immune cell infiltration levels across cancer types. The results are visualized as heatmaps. To improve the robustness of immune infiltration analyses, multiple immune deconvolution algorithms available in the SangerBox platform (<http://www.sangerbox.com>) were applied, including Tumor Immune Estimation Resource (TIMER) (41), Estimating the Proportions of Immune and Cancer cells (EPIC) (42), Quantification of the Tumor Immune Contexture from Human RNA-seq Data (quanTIseq) (43) and xCell (44). Correlations between UBE2A expression and immune cell infiltration were evaluated using these algorithms.

Tumor mutational burden (TMB) and microsatellite instability analysis (MSI). TCGA transcriptomic data, TMB data and MSI data were integrated for pan-cancer analysis. Spearman's correlation analysis was performed to evaluate the associations between UBE2A expression and TMB or MSI across different cancer types. Correlation coefficients and corresponding P-values were calculated using R software and the results are visualized as radar plots.

Single-cell analysis. Single-cell transcriptomic analysis was performed using the Tumor Immune Single-Cell Hub 2 (TISCH2) database, a comprehensive single-cell RNA-seq (scRNA-seq) resource for tumor microenvironment analysis (45). TISCH2 provides uniformly processed scRNA-seq datasets with standardized quality control, clustering, batch-effect correction and hierarchical cell-type annotation using the Model-based Analyses of Single-cell Transcriptome

and Regulome pipeline (45). In the present study, four breast cancer datasets, including BRCA_GSE114727 (46), BRCA_GSE110686 (47), BRCA_GSE148673 (48) and BRCA_GSE176078 (49), were analyzed to investigate the single-cell expression pattern of UBE2A in different cell populations within the tumor microenvironment. Cell annotations curated by TISCH2 were used at the malignancy, major-lineage and minor-lineage levels to ensure consistency and comparability across datasets. Gene expression distributions and cell-type-specific expression patterns were directly obtained and visualized through the TISCH2 platform.

Cell culture. MCF-10A, the human mammary epithelial cell line and breast cancer cell lines MCF-7, MDA-MB-231, MDA-MB-468 and Hs578T were purchased from Procell Life Science & Technology Co., Ltd. MCF-10A cells were cultured in DMEM/F12 medium, whereas breast cancer cell lines were maintained in DMEM medium. All media were supplemented with 10% FBS (Biological Industries; Sartorius AG) and 1% penicillin-streptomycin (Beijing Solarbio Science & Technology Co., Ltd.). Cells were cultured at 37°C in a humidified incubator containing 5% CO₂.

Reverse transcription-quantitative PCR (RT-qPCR) analysis. Total RNA was extracted from cultured breast epithelial and breast cancer cells lines, including MCF-10A, MCF-7, MDA-MB-231, MDA-MB-468 and Hs578T, using the Cell/Tissue Total RNA Kit (Suzhou Xinsaimai Biotechnology Co., Ltd.) following the manufacturer's protocol. RT was performed using HiScript III RT SuperMix (Vazyme Biotech Co., Ltd.) according to the manufacturer's protocol. RT-qPCR was carried out on the qTOWER3G system (Analytik Jena GmbH + Co. KG) with ChamQ Universal SYBR qPCR Master Mix (Vazyme Biotech Co., Ltd.) under the following thermocycling conditions: Initial denaturation at 95°C for 30 sec, followed by 40 cycles of denaturation at 95°C for 10 sec and annealing/extension at 60°C for 30 sec. β -actin was used as the internal reference gene for normalization and relative expression levels were calculated using the $2^{-\Delta\Delta C_q}$ method (50). The primer sequences are listed in Table SI.

Small interfering RNA (siRNA) transfection of cells. Targeted silencing of UBE2A was achieved using specific siRNA and corresponding scrambled negative control siRNA, all synthesized by Hanbio Biotechnology Co., Ltd. For siRNA transfection, MCF-7 and MDA-MB-231 cells in 6-well plates were transfected with 100 pmol siRNA per well using Lipofectamine™ 3000 (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol. Following 48 h of transfection, knockdown efficiency was validated at both mRNA and protein levels through qPCR and western blotting, respectively. The siRNA sequences are detailed in Table SII.

Cell Counting Kit-8 (CCK-8) assay. MCF-7 and MDA-MB-231 cells were seeded in 96-well plates at a density of 3,000 cells/well (100 μ l medium/well) with 5 technical replicates per group. After cell attachment (0 h), the medium was replaced with 100 μ l fresh complete medium containing 10% CCK-8 reagent (Vazyme Biotech Co., Ltd.) at 0, 24, 48 and 72 h, followed by incubation under standard culture

conditions for 2 h. Absorbance was measured at 450 nm using a microplate reader (BioTek; Agilent Technologies, Inc.). Cell viability was calculated and growth curves were plotted based on optical density values.

Wound healing assay. To evaluate cell migration capacity, pre-marked reference lines were drawn on the bottom of 6-well plates prior to cell seeding. MCF-7 and MDA-MB-231 cells were cultured in complete medium until reaching 95–100% confluence. A wound was created by scratching the monolayer with a 200 μ l sterile pipette tip perpendicular to the reference lines. After washing with PBS to remove detached cells, fresh serum-free medium was added. Wound areas were photographed at 0 and 24 h post-scratching using an inverted phase-contrast microscope (Olympus-IX71; Olympus Corporation). ImageJ (National Institutes of Health; version 1.53a) was used to calculate the scratch area.

Transwell assay. For migration assays, MCF-7 and MDA-MB-231 cells (5×10^4 cells per well) were suspended in 100 μ l serum-free medium and seeded into the upper chamber of Transwell inserts (Corning, Inc.). The lower chamber was filled with 800 μ l complete medium containing 10% FBS (Biological Industries; Sartorius AG) as a chemoattractant. For invasion assays, transwell inserts were pre-coated with Matrigel (Shanghai Yeasen Biotechnology Co., Ltd.) and incubated at 37°C for 2 h before cell seeding. Cells were then incubated at 37°C in a humidified atmosphere containing 5% CO₂ for 24 h. After incubation, non-migrated cells were removed from the upper surface of the membrane using cotton swabs. Cells that had migrated or invaded to the lower surface were fixed with fixed with 4% paraformaldehyde (Beijing Solarbio Science & Technology Co., Ltd.) at room temperature for 20 min and stained with 0.1% crystal violet (Beyotime Biotechnology) at room temperature for 20 min. Images were captured using an inverted microscope (Olympus IX73; Olympus Corporation) and cell numbers were quantified using ImageJ software.

Western blotting. Total cellular proteins were extracted from MCF-7 and MDA-MB-231 cells using a column-based total protein extraction kit (Suzhou Xinsaimai Biotechnology Co., Ltd.) and protein concentrations were determined by a BCA assay (Beyotime Biotechnology). Equal quantities of protein (30 μ g per lane) were separated by 10% SDS-PAGE and subsequently transferred onto PVDF membranes (MilliporeSigma; Merck KGaA). Following transfer, membranes were blocked with 5% non-fat milk at room temperature for 1 h and then incubated with the indicated primary antibodies at 4°C overnight. After washing, membranes were probed with HRP-conjugated secondary antibodies for 1 h at room temperature. Immunoreactive signals were detected using an ECL detection system (Thermo Fisher Scientific, Inc.) and captured with an imaging system from e-BLOT Life Science (Shanghai) Co., Ltd. The antibodies used included anti-UBE2A (1:1,000; cat. no. sc-365507; Santa Cruz Biotechnology, Inc.), anti- β -actin (1:20,000; cat. no. 66009-1-Ig; Proteintech Group, Inc.), HRP-conjugated goat anti-rabbit IgG (1:10,000; cat. no. SA00001-2; Proteintech Group, Inc.) and HRP-conjugated goat anti-mouse IgG (1:10,000 cat. no. SA00001-1; Proteintech Group, Inc.).

Statistical analysis. Statistical analyses were performed using GraphPad Prism (version 10.1.2; Dotmatics) and R software. Differences between groups were evaluated using unpaired Student's t-test or one-way ANOVA, as appropriate. Unless otherwise specified, two-sided $P < 0.05$ was considered to indicate a statistically significant difference. For bioinformatic analyses, statistical testing and multiple-testing correction were performed according to the corresponding analytical pipelines and false discovery rate-adjusted P-values were applied in enrichment analyses.

Results

UBE2A shows differential expression across several cancers. To characterize the expression profile of UBE2A across human cancers, TCGA transcriptomic datasets were analysed and UBE2A expression was compared between tumor tissues and corresponding normal tissues. As shown in Fig. 2A, UBE2A expression was found to be significantly elevated in bladder urothelial carcinoma (BLCA), BRCA, cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), cholangiocarcinoma (CHOL), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), stomach adenocarcinoma (STAD) and thyroid carcinoma (THCA) compared with corresponding normal tissues. By contrast, kidney chromophobe (KICH) exhibited significantly lower UBE2A expression. To further validate these findings, an integrated analysis combining TCGA tumor samples and GTEx normal tissues was performed. Consistent with the TCGA-based analysis, UBE2A remained significantly upregulated in BLCA, BRCA, CESC, CHOL, ESCA, GBM, HNSC, LIHC, LUAD, LUSC, STAD and THCA. In addition, further cancer types with significant dysregulation were identified after incorporating GTEx normal tissues, resulting in elevated UBE2A expression in 25 cancer types and reduced expression in five cancer types overall (Fig. 2B). In addition, paired tumor-normal analyses within TCGA cohorts further demonstrated significantly elevated UBE2A expression in BLCA, BRCA, CHOL, ESCA, HNSC, LIHC, LUAD, LUSC, STAD and THCA, while significantly reduced expression was observed in KICH (Fig. 2C). By contrast, no significant differences were detected in CESC, COAD, KIRC, KIRP, PAAD, PCPG, PRAD, READ or UCEC.

To further assess the robustness of these observations, two independent breast cancer cohorts from the GEO database (GSE29044 and GSE65194) were analyzed. Consistent with the TCGA results, UBE2A expression was found to be significantly increased in breast cancer tissues compared with normal breast tissues in both datasets (Fig. 2D and E). Collectively, these findings demonstrate that UBE2A is aberrantly upregulated in a broad spectrum of human cancer types, particularly in breast cancer, suggesting that UBE2A may serve an important role in tumor development and progression.

UBE2A is associated with clinicopathological features in pan-cancer. To investigate the clinical relevance of UBE2A, its association with clinicopathological characteristics was evaluated across numerous cancer types. Analysis of tumor invasion status revealed significant differences in UBE2A

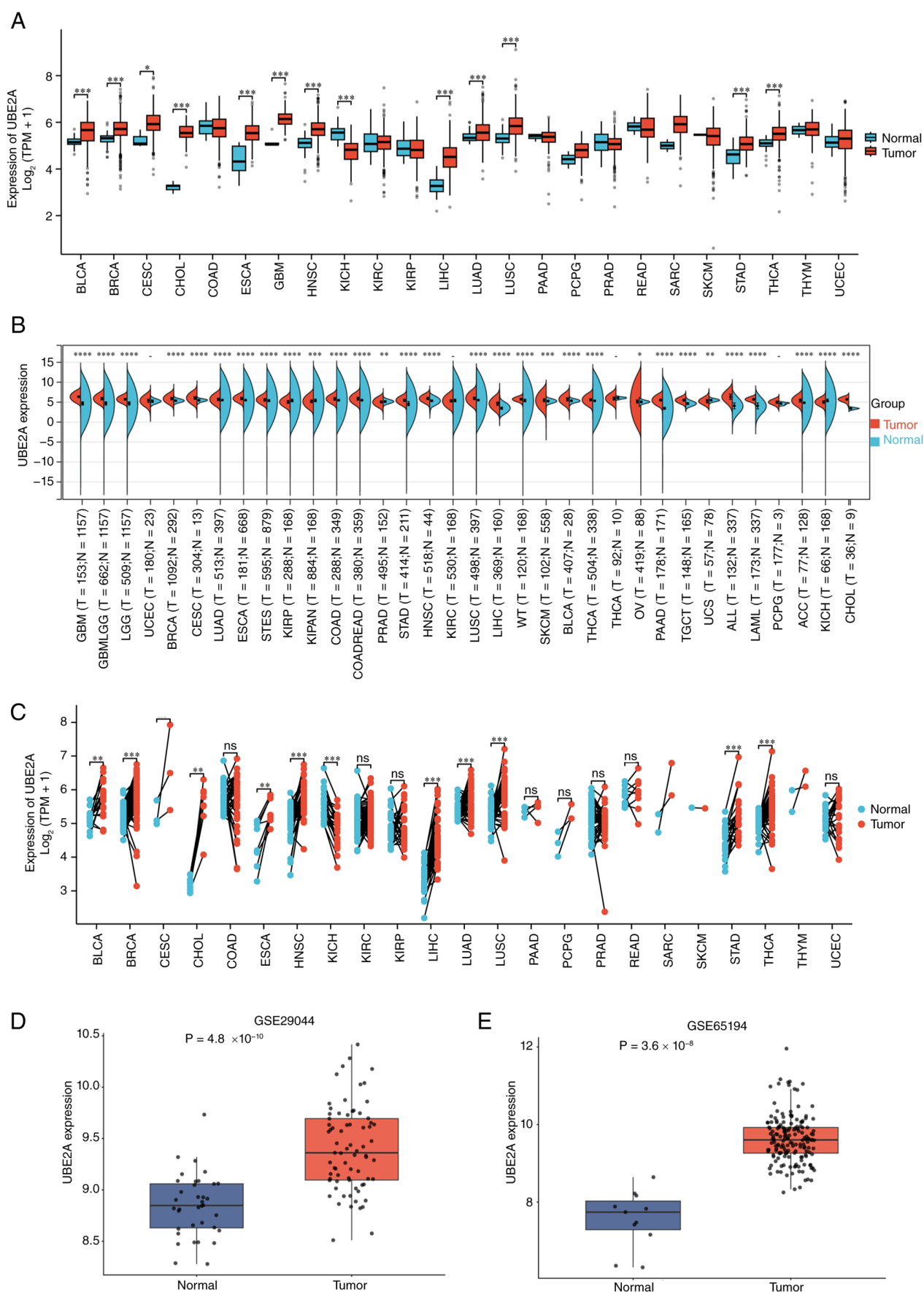


Figure 2. Expression landscape of UBE2A across human cancers. (A) Differential expression analysis of UBE2A between tumor and normal tissues across TCGA cancer types. (B) UBE2A expression profiles based on integrated TCGA and Genotype-Tissue Expression Project datasets. (C) Paired comparison of UBE2A expression between tumor tissues and matched adjacent normal tissues in TCGA cohorts. (D) Independent validation of UBE2A expression in the breast cancer cohort GSE29044. (E) Independent validation of UBE2A expression in the breast cancer cohort GSE65194. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ and **** $P < 0.0001$. UBE2A, ubiquitin conjugating enzyme E2A; TCGA, The Cancer Genome Atlas; TPM, transcripts per million; ns, not significant.

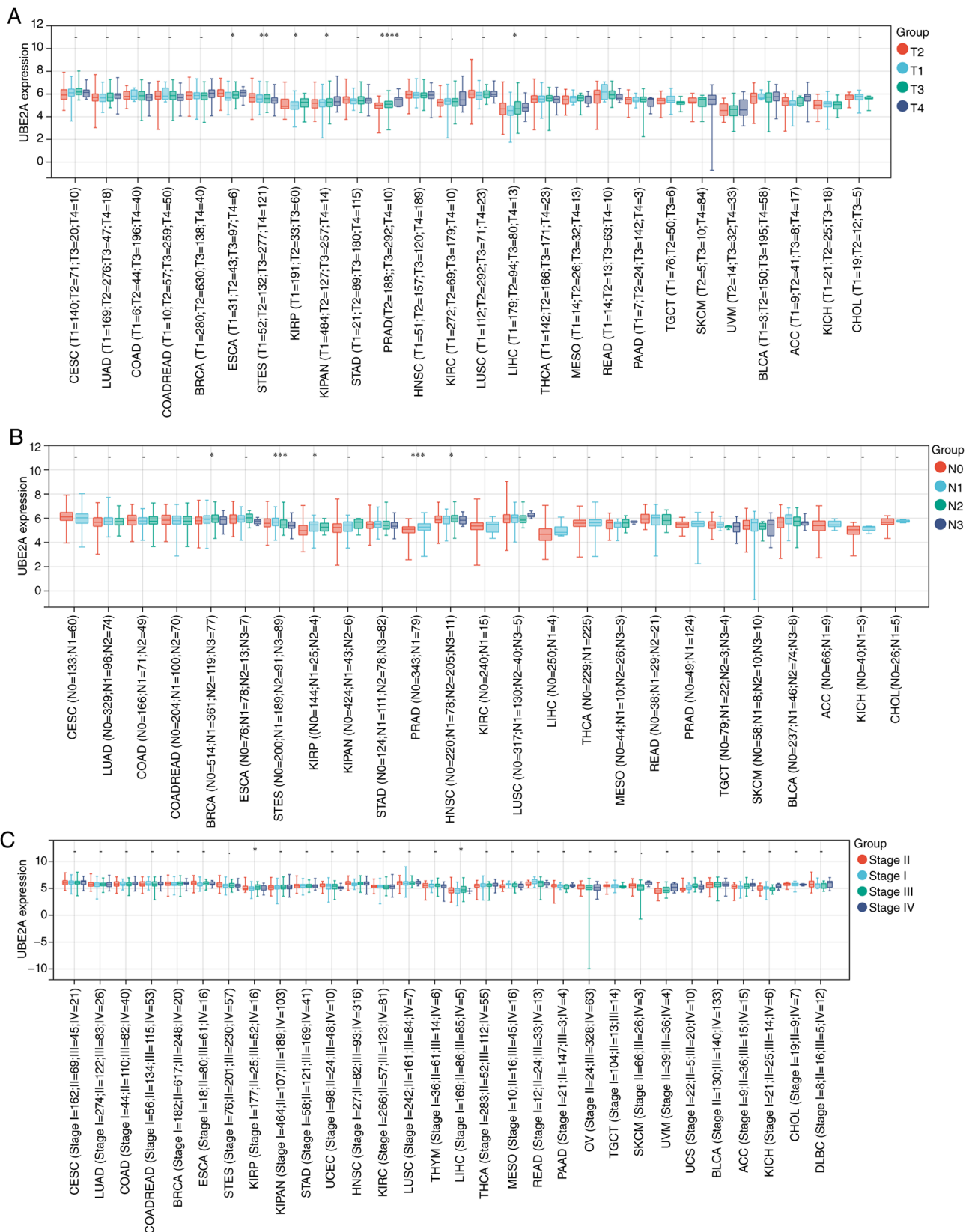


Figure 3. Associations between UBE2A expression and clinicopathological parameters in pan-cancer analysis. (A) Distribution of UBE2A expression across different T stages in selected cancer types. (B) Association between UBE2A expression and N stage across cancer types. (C) UBE2A expression according to integrated TNM stage in pan-cancer cohorts. * $P<0.05$, ** $P<0.01$, *** $P<0.001$ and **** $P<0.0001$. UBE2A, ubiquitin conjugating enzyme E2A.

expression among T-stage subgroups in ESCA, STES, KIRP, pan-kidney cohort, PRAD and LIHC (Fig. 3A). With regard to lymph node metastasis, UBE2A expression was found to be

significantly associated with N stage in BRCA, STES, KIRP, PRAD and HNSC (Fig. 3B). Furthermore, significant correlations between UBE2A expression and overall pathological

stage were observed in KIRP and LIHC (Fig. 3C). These findings suggest that UBE2A expression is associated with tumor progression in numerous malignancies. Notably, the significant association between UBE2A expression and N stage in BRCA indicates a potential role for UBE2A in breast cancer progression and metastasis.

UBE2A exhibits diagnostic value across multiple cancer types. Diagnostic values of UBE2A expression were evaluated across a number of cancer types using ROC curve analysis. UBE2A exhibited good discriminatory ability between tumor and normal tissues in 15 cancer types (Fig. 4A-O). Notably, excellent diagnostic performance was observed in CHOL, esophageal adenocarcinoma (ESAD), ESCA, GBM, KICH and LIHC, with AUC values exceeding 0.90. These findings indicate that UBE2A expression may serve as a potential diagnostic biomarker in selected malignancies.

UBE2A is associated with prognosis across human cancers. To evaluate the prognostic relevance of UBE2A across cancers, survival analyses were performed using OS and DFS endpoints. Elevated UBE2A expression was significantly associated with shorter OS in BRCA, low-grade glioma (LGG), LIHC, mesothelioma, sarcoma (SARC) and uveal melanoma (UVM; Fig. 5A-G). Similarly, patients with high UBE2A expression exhibited significantly worse DFS in LGG, LIHC and UVM (Fig. 5H-K). To further validate these findings, independent BRCA cohorts were analyzed using the Kaplan-Meier Plotter platform. Consistent with the pan-cancer findings, elevated UBE2A expression was associated with unfavorable OS, RFS and DMFS (Fig. 5L-N). Collectively, these results suggest that UBE2A may represent a prognostic indicator in a number of malignancies, with reproducible associations observed across different survival endpoints and analytical platforms.

UBE2A displays distinct genetic alteration patterns across pan-cancer. Genomic alteration landscapes of UBE2A were next investigated across human cancers. UBE2A alterations were detected in ~1.1% of all analyzed tumors, although notable heterogeneity was observed among cancer types (Fig. 6A). The highest alteration frequency occurred in mature B-cell neoplasms (>10%), followed by endometrial carcinoma and non-small cell lung cancer, each exhibiting alteration frequencies of ~2% (Fig. 6B). Analysis of mutation patterns revealed that missense mutations were the predominant alteration type, with recurrent mutations affecting the R140 residue identified as hotspot events (Fig. 6C). Copy number gain represented the most common copy number alteration (Fig. 6D). Furthermore, tumors harboring UBE2A alterations exhibited significantly higher mutation frequencies of cystatin SN, SLC51 subunit β , ATPase inhibitory factor 1 and a number of additional genes compared with UBE2A wild-type tumors (Fig. 6E), suggesting that UBE2A alterations may co-occur with specific genomic events during tumor evolution.

UBE2A is linked to cancer-associated co-expression and protein interaction networks. To gain insight into the biological functions associated with UBE2A, genes correlated with UBE2A expression were identified and analyzed. The top 50 positively and negatively correlated genes are visualized as

heatmaps (Fig. 7A and B). Functional enrichment analyses based on the top 500 UBE2A-associated genes revealed significant enrichment in ‘chromosome segregation’, ‘mitotic cell cycle phase transition’ and other cell cycle-associated biological processes (Fig. 7C). Consistently, KEGG pathway analysis identified significant enrichment of ‘proteasome’ and ‘cell cycle’ pathways (Fig. 7D).

To further characterize biological pathways associated with UBE2A expression, GSEA was performed in BRCA. GO-based GSEA identified enrichment of ‘GOMG_OLFACTORY_RECEPTOR_ACTIVITY’, amongst other terms, whereas KEGG-based GSEA demonstrated significant enrichment of ‘KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION’ as well as ‘KEGG_CYTOSOLIC_DNA_SENSING_PATHWAY’ in the UBE2A high-expression group (Fig. 7E). In addition, a PPI network centered on UBE2A revealed numerous closely connected interacting proteins and functional modules (Fig. 7F), supporting the potential involvement of UBE2A in cell cycle regulation and proteostasis-associated processes.

UBE2A is associated with DNA and RNA methylation patterns in pan-cancer. To investigate potential epigenetic mechanisms underlying UBE2A dysregulation, promoter methylation patterns were analyzed across multiple cancer types. Compared with normal tissues, a significantly lower promoter methylation levels of UBE2A was observed in BLCA, LIHC, BRCA and STAD (Fig. 8A-D). By contrast, significantly increased promoter methylation was detected in PRAD (Fig. 8E). The association between UBE2A expression and RNA modification regulators was further examined. UBE2A expression exhibited significant correlations with numerous RNA modification-associated genes across cancer types, particularly a number m6A regulators, including methyltransferase-like 14 and Wilms tumor 1-associating protein (Fig. 8F). Collectively, these findings suggest that epigenetic mechanisms may contribute to the dysregulated expression of UBE2A in human cancers.

Differential expression of UBE2A among immune and molecular subtypes in 33 malignancies. Whether UBE2A expression differed among distinct molecular and immune subtypes across cancers was next examined. Significant differences in UBE2A expression among molecular subtypes were observed in BRCA, COAD, HNSC, KIRP, LGG, LUSC, ovarian cancer (OV) and pheochromocytoma and paraganglioma (Fig. 9A-H). Similarly, UBE2A expression varied markedly among immune subtypes in 12 cancer types (Fig. 9I-T). These observations indicated that UBE2A expression may be associated with tumor heterogeneity at both molecular and immune levels.

UBE2A is associated with immune infiltration and genomic instability in pan-cancer. To explore potential associations between UBE2A expression and the tumor immune micro-environment, correlations between UBE2A expression and immune cell infiltration were evaluated across cancers. UBE2A expression exhibited significant correlations with numerous immune cell populations in different tumor types, including resting memory CD4⁺ T cells, activated memory CD4⁺ T cells, activated NK cells and M2 macrophages (Fig. 10A). Similar

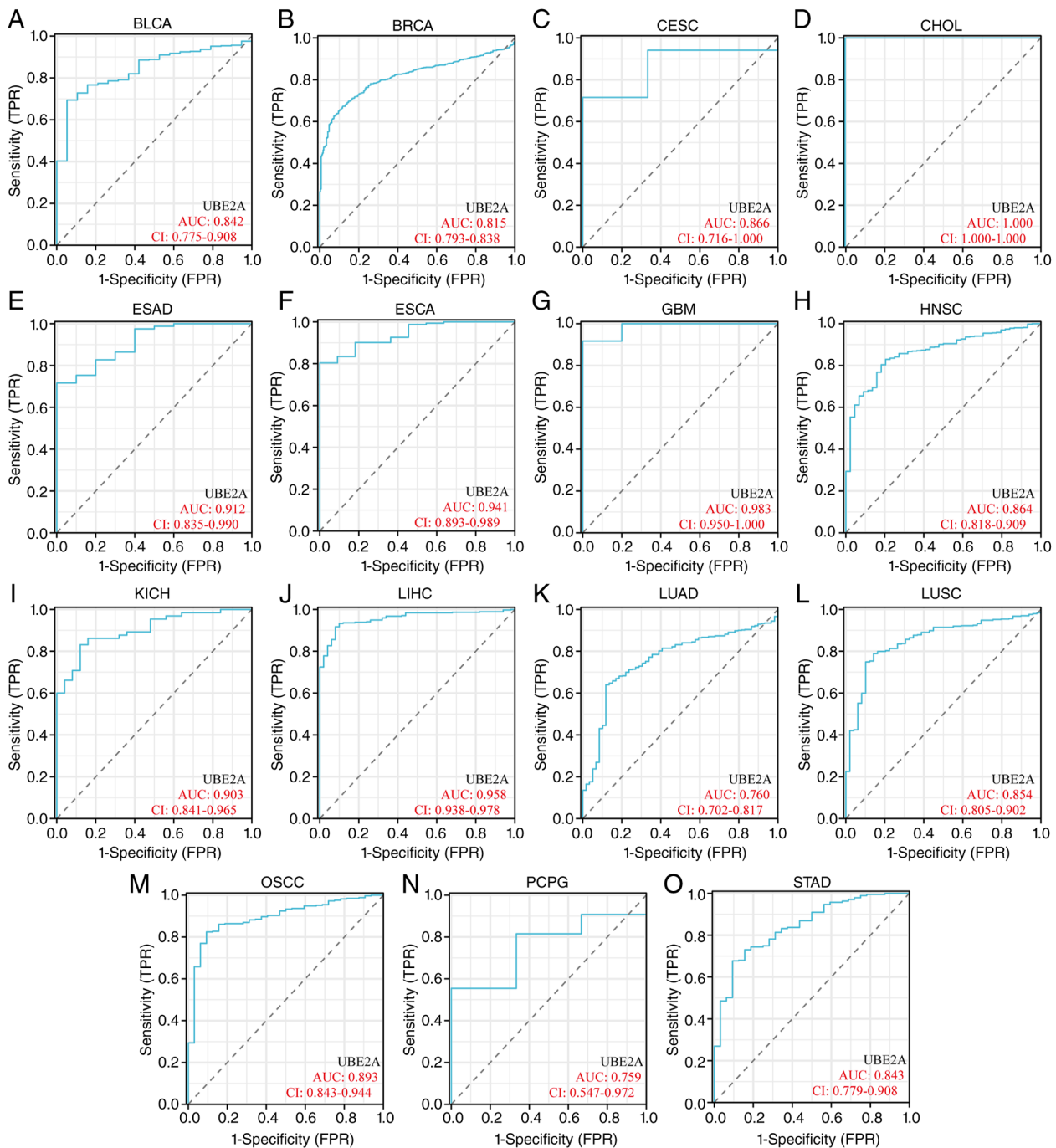


Figure 4. Diagnostic performance of UBE2A expression across cancer types. Receiver operating characteristic (ROC) curves evaluating the ability of UBE2A expression to distinguish tumor tissues from normal tissues in (A) BLCA, (B) BRCA, (C) CESC, (D) CHOL, (E) ESAD, (F) ESCA, (G) GBM, (H) HNSC, (I) KICH, (J) LIHC, (K) LUAD, (L) LUSC, (M) OSCC, (N) PCPG and (O) STAD. UBE2A, ubiquitin conjugating enzyme E2A; ROC, receiver operating characteristic; AUC, area under the curve; FPR, false positive rate; TRP, true positive rate.

trends were observed when additional immune deconvolution algorithms, including EPIC, QUANTISEQ, TIMER and xCELL, were applied (Fig. S1A-D). The associations between UBE2A expression and immune regulatory genes were further examined. UBE2A expression exhibited widespread correlations with numerous immunomodulatory molecules, including C-X-C motif chemokine ligand 10 and IL-10, across cancer types (Fig. S2). In addition, significant associations were observed between UBE2A expression and a number of immune checkpoint-associated genes, including IL-12A and TGF- β 1 (Fig. S3).

Given the clinical relevance of genomic instability in immunotherapy, correlations between UBE2A expression and TMB or MSI were subsequently analyzed (51,52). UBE2A expression was found to be positively associated with TMB in BLCA, BRCA, LGG, OV, PRAD, SARC and STAD, whereas negative correlations were observed in COAD, KIRP and thymoma (Fig. 10B). For MSI, positive correlations were detected in adrenocortical carcinoma, HNSC, PRAD, SARC, STAD, tenosynovial giant cell tumor and THCA, while negative associations were observed in COAD, diffuse large B-cell lymphoma, LUAD, LUSC and OV (Fig. 10C). Collectively,

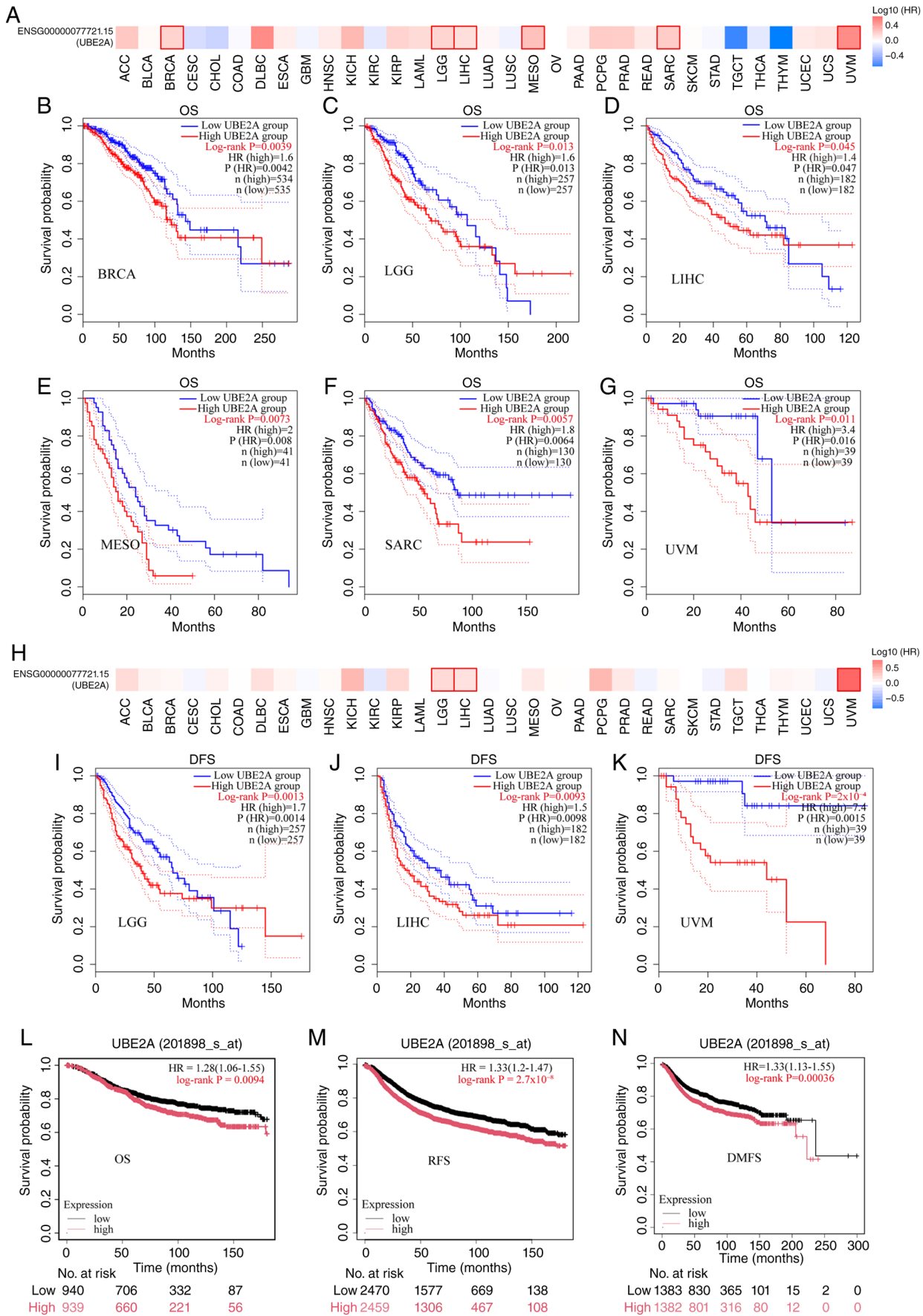


Figure 5. Prognostic relevance of UBE2A expression across human cancers. (A) Overview of the associations between UBE2A expression and OS across TCGA cancer types. Kaplan-Meier analysis of OS in (B) BRCA, (C) LGG, (D) LIHC, (E) MESO, (F) SARC and (G) UVM. (H) Overview of the associations between UBE2A expression and DFS across TCGA cancer types. Kaplan-Meier analysis of DFS in (I) LGG, (J) LIHC and (K) UVM. (L) Kaplan-Meier Plotter validation of OS in BRCA. (M) Kaplan-Meier Plotter validation of RFS in BRCA. (N) Kaplan-Meier Plotter validation of DMFS in BRCA. UBE2A, ubiquitin conjugating enzyme E2A; OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; HR, hazard ratio.

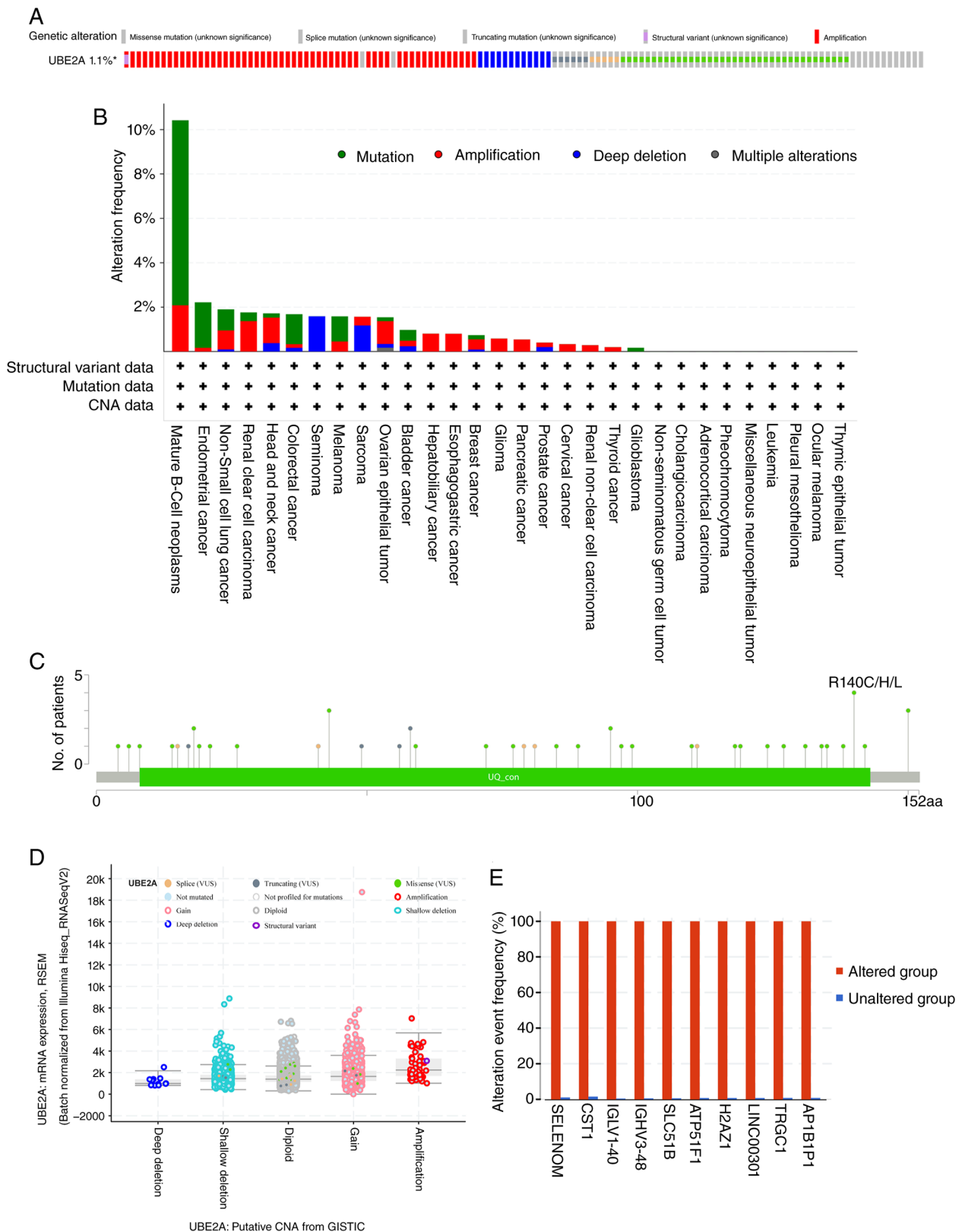


Figure 6. Genomic landscape of UBE2A aberrations across cancer types. (A) Overall mutation frequency of UBE2A across all cancer types. (B) Frequency of UBE2A alterations across different tumor types. (C) Mutation site distribution in UBE2A. (D) Classification of UBE2A alteration types. (E) Co-mutation analysis of UBE2A and associated genes. UBE2A, ubiquitin conjugating enzyme E2A; CNA, copy number alteration; RSEM, RNA-Seq by expectation-maximization; VUS, variant of uncertain significance; GISTIC, genomic identification of significant targets in cancer.

these findings suggest that UBE2A expression may be associated with distinct immune and genomic features in a cancer type-dependent manner.

Single-cell analysis reveals cell-type-specific expression of UBE2A. Single-cell omics technologies enable high-resolution profiling of tumor heterogeneity by capturing cell-to-cell

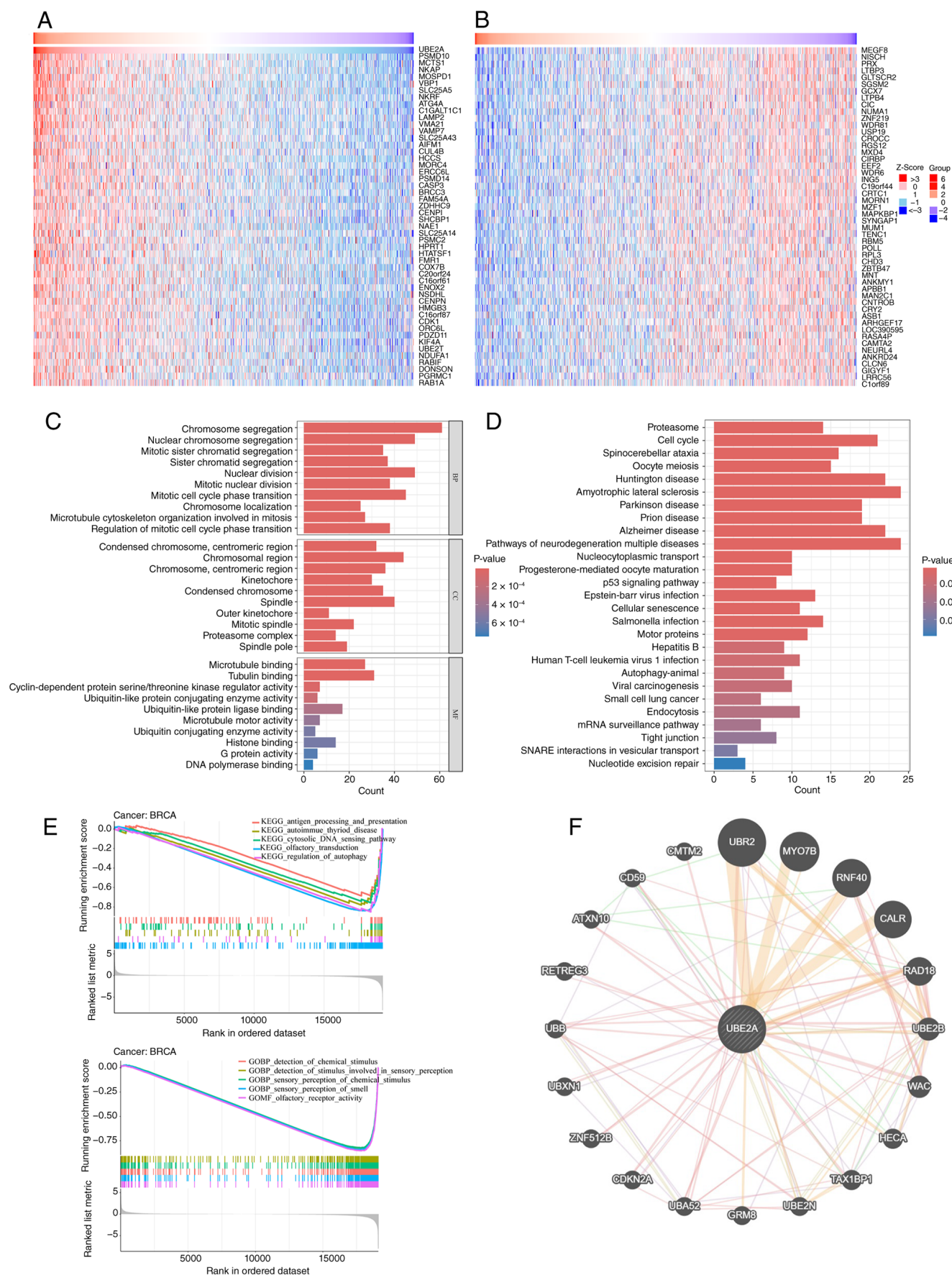


Figure 7. Co-expression analysis, functional enrichment and PPI network of UBE2A. Heatmaps showing the top 50 genes positively (A) and negatively (B) correlated with UBE2A expression. (C) GO enrichment analysis of UBE2A co-expressed genes. (D) KEGG pathway enrichment analysis of UBE2A-associated gene sets. (E) Gene Set Enrichment Analysis comparing high and low UBE2A expression groups in the BRCA cohort. (F) PPI network of UBE2A generated using GeneMANIA. UBE2A, ubiquitin conjugating enzyme E2A; PPI, protein-protein interaction; GO, Gene Ontology; GOBP, GO biological process; GOMF, GO molecular function; KEGG, Kyoto Encyclopedia of Genes and Genomes.

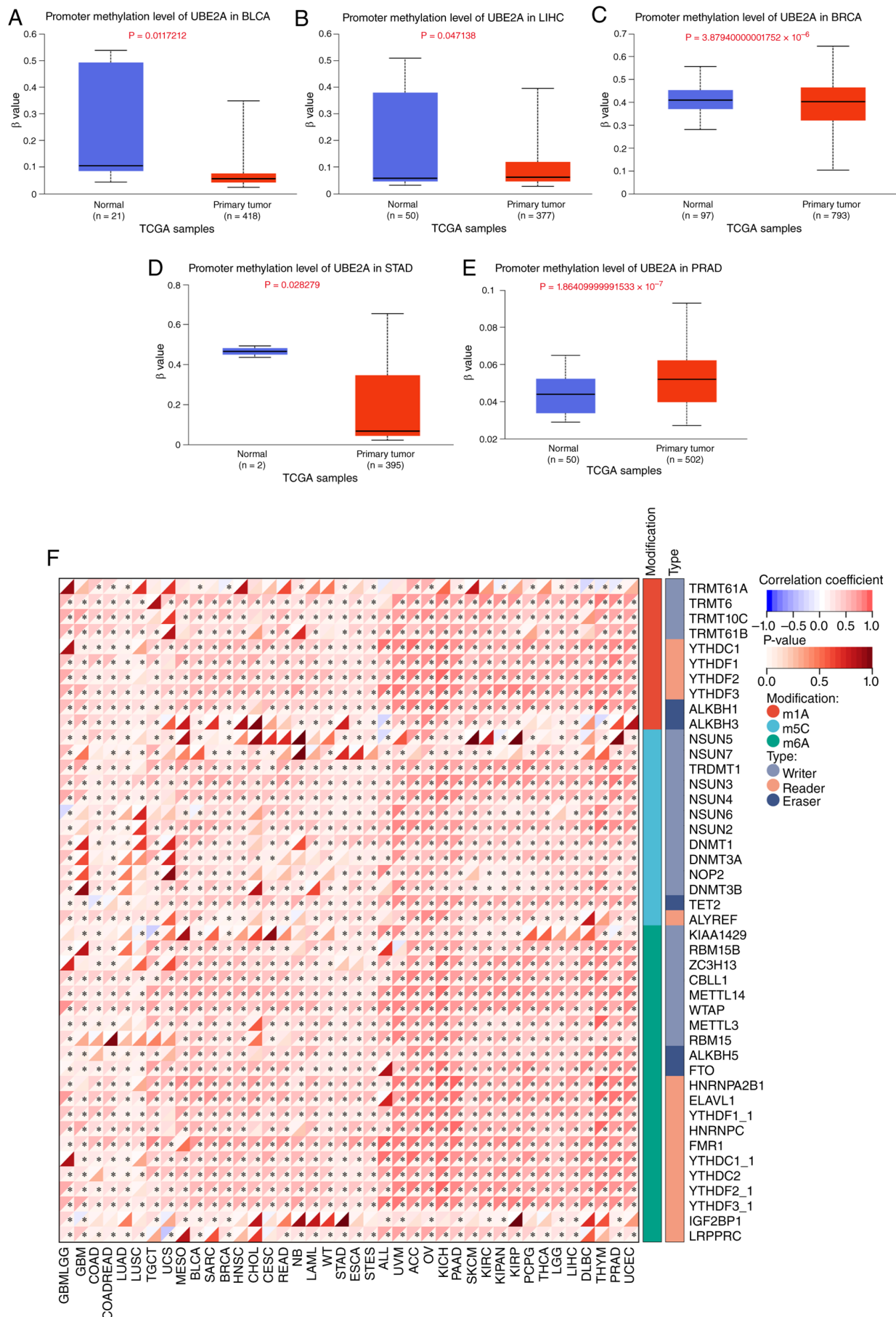


Figure 8. DNA promoter methylation and mRNA methylation analysis of UBE2A across human cancers. Promoter methylation levels of UBE2A in (A) BLCA, (B) LIHC, (C) BRCA, (D) STAD and (E) PRAD from the University of Alabama at Birmingham Cancer Data Analysis Portal database. (F) Correlation between UBE2A expression and RNA methylation-associated genes across cancers. * $P < 0.05$. UBE2A, ubiquitin conjugating enzyme E2A; TCGA, The Cancer Genome Atlas.

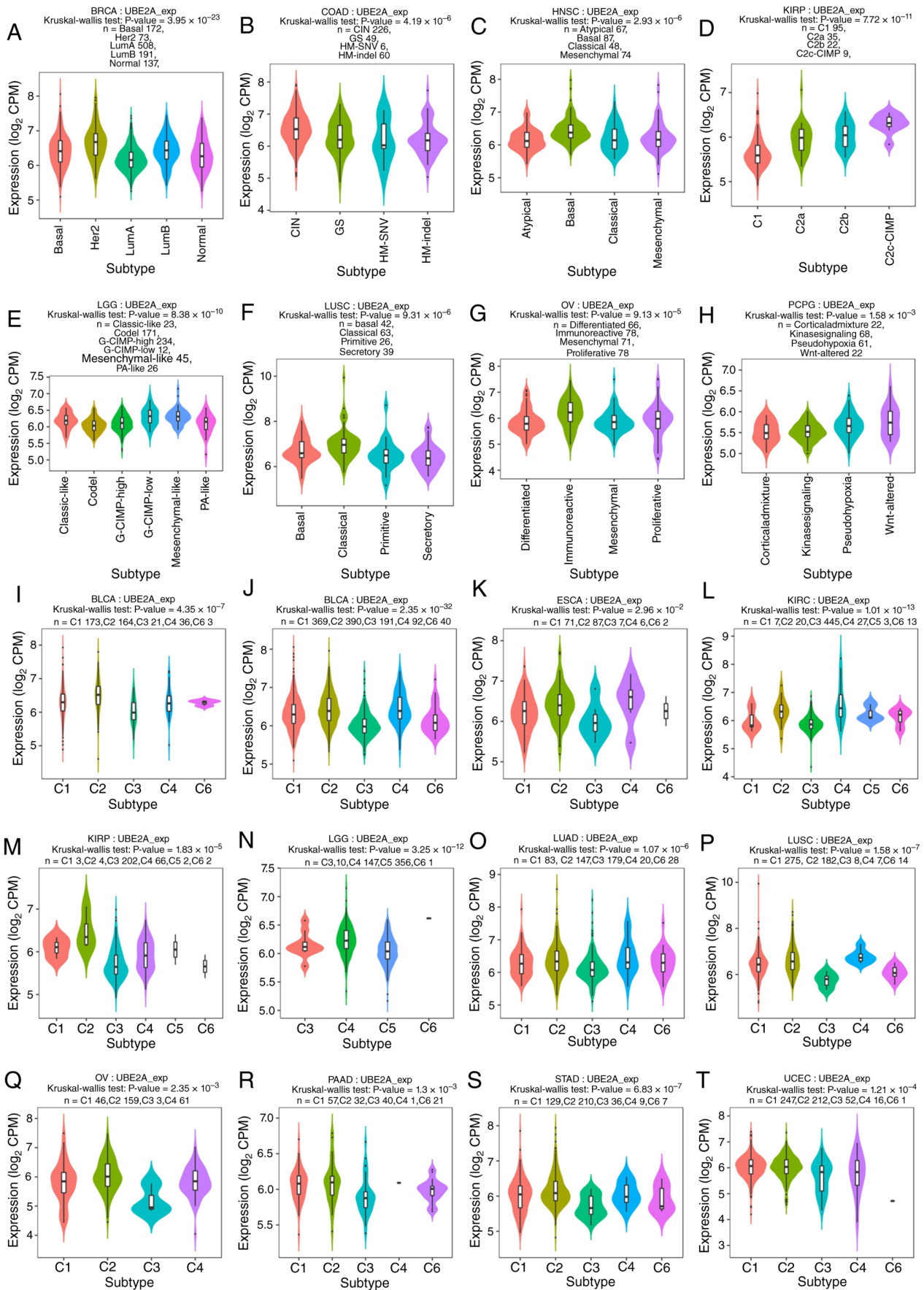


Figure 9. UBE2A expression patterns across molecular and immune subtypes in 33 cancer types. (A-H) UBE2A expression among molecular subtypes in (A) BRCA, (B) COAD, (C) HNSC, (D) KIRP, (E) LGG and (F) LUSC, (G) OV and (H) PCPG. (I-T) UBE2A expression profiles across immune subtypes in (I) BLBA, (J) BRCA, (K) ESCA, (L) KIRC, (M) KIRP, (N) LGG, (O) LUAD, (P) LUSC, (Q) OV, (R) PAAD, (S) STAD and (T) UCEC. UBE2A, ubiquitin conjugating enzyme E2A; Lum, luminal; CIN, chromosomal instability; GS, genomically stable; HM, hypermutated; SNV, single nucleotide variant; indel, insertion/deletion; G-CIMP, glioma CpG island methylator phenotype.

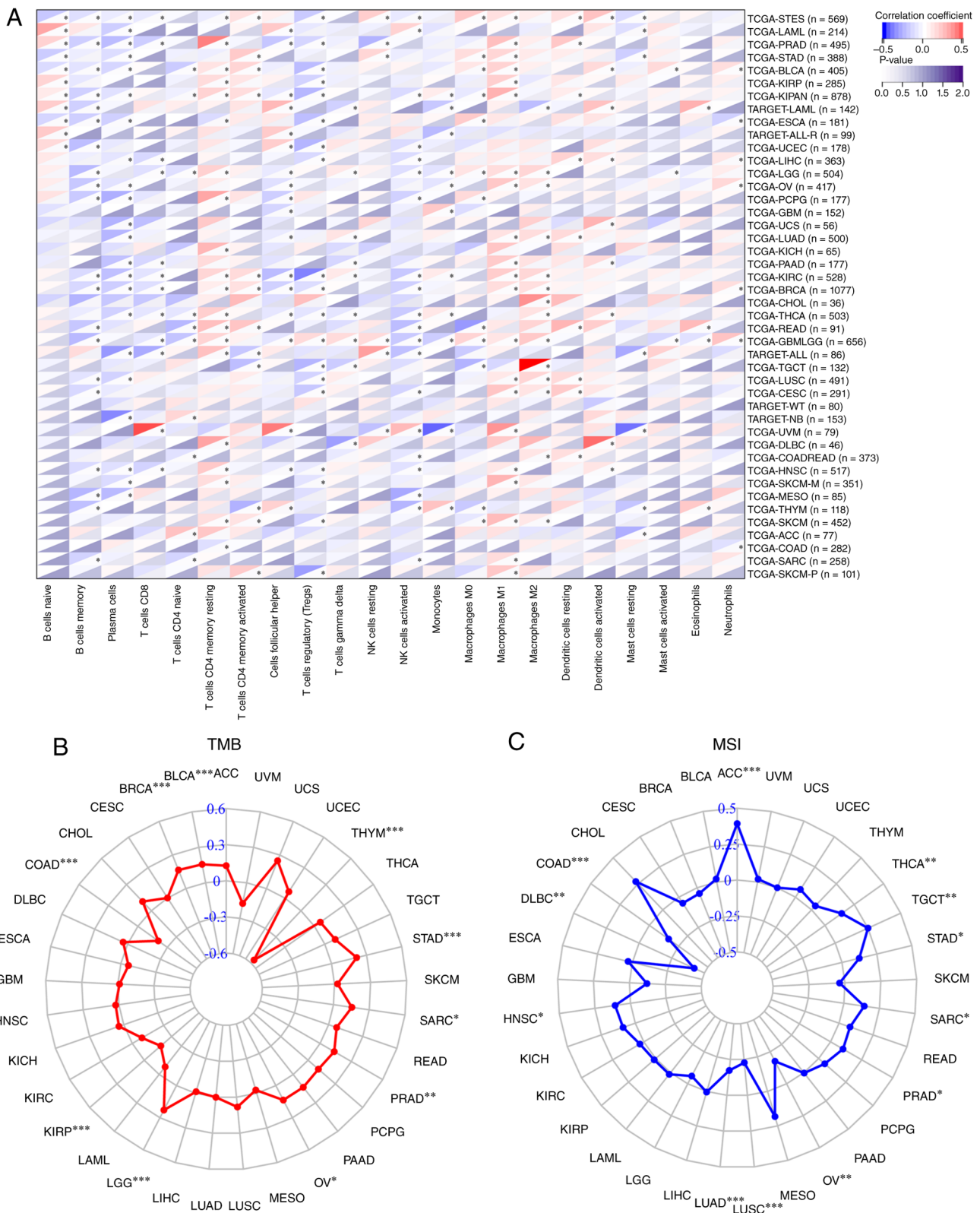


Figure 10. Associations of UBE2A expression with the immune microenvironment, TMB and MSI across cancers. (A) Heatmap showing the correlation between UBE2A expression and infiltration levels of 22 immune cell types across various cancers. (B) Correlation analysis between UBE2A expression and TMB in pan-cancer. (C) Correlation between UBE2A expression and MSI across cancers. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$. UBE2A, ubiquitin conjugating enzyme E2A; TMB, tumor mutational burden; MSI, microsatellite instability.

variability that is masked by traditional bulk sequencing, thereby advancing precision oncology and improving our understanding of tumor biology (53,54). To further characterize the cellular distribution of UBE2A within the tumor

microenvironment, single-cell RNA-seq datasets from four independent BRCA cohorts were analyzed. Across all datasets, UBE2A expression was found to be predominantly enriched in the proliferative T-cell population (Fig. 11A-E).

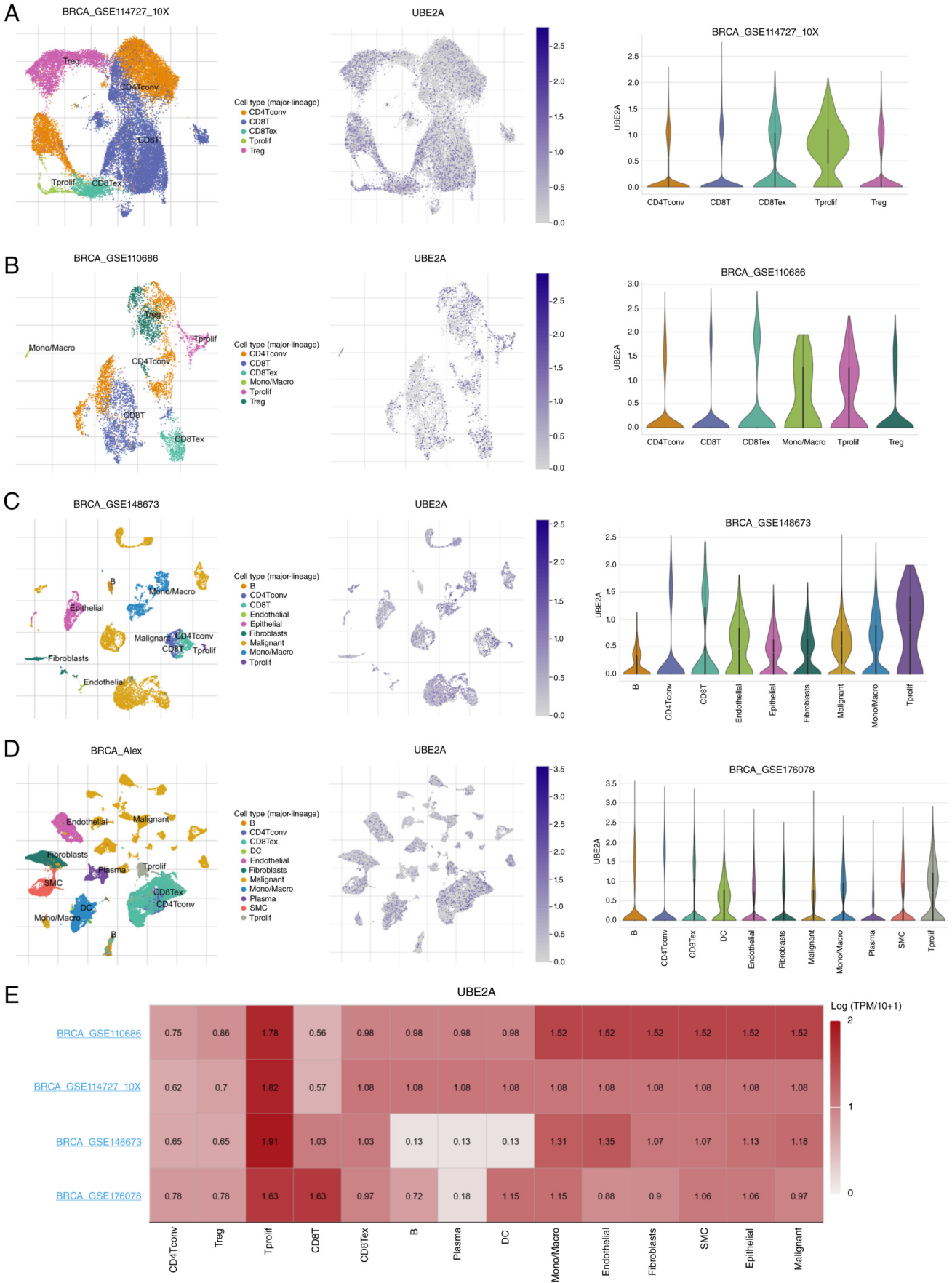


Figure 11. Single-cell transcriptomic characterization of UBE2A expression in breast cancer. Uniform Manifold Approximation and Projection and Violin plots showing the expression levels of UBE2A across different cellular subpopulations in BRCA single-cell RNA sequencing datasets (A) GSE114727, (B) GSE110686, (C) GSE148673 and (D) GSE176078. (E) UBE2A expression landscape across cellular subpopulations, highlighting preferential expression in proliferative T-cell populations. UBE2A, ubiquitin conjugating enzyme E2A; TPM, transcripts per million; DC, dendritic cell; SMC, smooth muscle cell; conv, conventional T cell; ex, exhausted T cell; Tprolif, proliferative T-cell; Treg, regulatory T-cell.

Consistent expression patterns across independent datasets indicated a potential association between UBE2A expression and proliferative T-cell states within the breast tumor microenvironment. Notably, these observations were derived from transcriptomic datasets and therefore should be considered hypothesis-generating findings that require further experimental validation.

UBE2A deficiency suppresses migration, proliferation and invasion of breast cancer cells in vitro. Based on the pan-cancer analysis results, breast cancer was selected for functional validation as UBE2A exhibited significant upregulation and prognostic relevance in BRCA. In addition, the present bioinformatic analyses suggested a potential involvement of UBE2A in tumor progression and tumor microenvironment regulation in breast cancer. Therefore, the biological functions of UBE2A in breast cancer cell lines were further investigated. qPCR analysis demonstrated differential UBE2A expression among breast cancer cell lines. Compared with the normal breast epithelial cell line MCF-10A, UBE2A expression was significantly elevated in MCF-7, MDA-MB-231 and MDA-MB-468 cells (Fig. 12A). Based on their relatively high expression levels, MCF-7 and MDA-MB-231 cells were selected for subsequent functional experiments.

A total of three siRNAs targeting UBE2A were designed and transfected into MCF-7 and MDA-MB-231 cells. qPCR and western blotting analyses demonstrated that all three siRNAs significantly reduced UBE2A expression (Fig. 12B-G), with siUBE2A#1 and siUBE2A#2 exhibiting the strongest knock-down efficiency; thus, these two sequences were chosen for subsequent experiments. CCK-8 assays revealed that UBE2A silencing significantly inhibited cell proliferation in both lines, compared with the negative control (Fig. 12H and I). Wound healing assays further indicated a significant reduction in migration capacity upon UBE2A knockdown, compared with the negative control (Fig. 13A-D). Lastly, Transwell assays demonstrated that UBE2A knockdown significantly impaired both migration and invasion abilities in MCF-7 and MDA-MB-231 cells (Fig. 13E-J).

Discussion

Cancer continues to represent a major global health challenge owing to its high morbidity, mortality and biological complexity (55,56). Despite notable advances in early detection and therapeutic interventions, numerous aspects of tumor initiation and progression remain insufficiently defined, largely due to the extensive inter- and intra-tumoral heterogeneity observed across cancer types (57). This complexity poses marked barriers to durable therapeutic efficacy and underscores the importance of identifying molecular determinants that are conserved across cancers while retaining tumor-type specificity. Pan-cancer analytical strategies provide a valuable framework for addressing these challenges by enabling the systematic interrogation of oncogenic processes across a number of malignancies, encompassing tumor heterogeneity, evolutionary trajectories and interactions with the tumor microenvironment (11). By integrating multi-omics datasets, pan-cancer analyses can uncover shared molecular programs as well as context-dependent features that may not be apparent in single-cancer investigations.

Within this framework, the present study sought to characterize the pan-cancer landscape of UBE2A and to explore its potential biological and clinical relevance.

Although UBE2A has been implicated in the progression of a number of malignancies, including HCC, OV, melanoma and multiple myeloma (58-61), its expression profile and regulatory features across a broad spectrum of cancers have not been systematically evaluated. Using integrated TCGA and GTEx datasets, it was observed that UBE2A expression exhibited marked heterogeneity across tumor types, with notable upregulation in the majority of cancers, including GBM, BRCA and STAD, as well as downregulation in a limited subset such as KIRC. This pattern suggests that UBE2A expression may be subject to tissue- or lineage-specific regulatory constraints. Epigenetic analyses further indicated that reduced promoter DNA methylation was associated with elevated UBE2A expression in certain cancer types, including BLCA, LIHC, BRCA and STAD, consistent with the established role of promoter hypomethylation in transcriptional activation (62). However, in other tumor types, differential expression of UBE2A occurred in the absence of corresponding methylation changes, implying that additional regulatory mechanisms, such as histone modifications, transcription factor binding or post-transcriptional regulation, may contribute to its context-dependent expression. These findings highlight the complexity of UBE2A regulation and suggest that epigenetic control alone does not fully account for its dysregulation in cancer.

From a clinical perspective, elevated UBE2A expression was found to be associated with unfavorable OS and DFS in numerous malignancies, including breast cancer. While previous studies have reported the prognostic relevance of UBE2A in individual cancer types (18,22), the present pan-cancer approach extended these observations by providing a broader and more systematic assessment across diverse tumor contexts. In addition to its prognostic implications, UBE2A demonstrated notable diagnostic performance in a number of cancer types, with strong discriminatory capacity observed in CHOL, ESAD, ESCA, GBM, KICH and LIHC. These findings suggest that aberrant UBE2A expression may reflect underlying oncogenic processes that are detectable at the transcriptomic level. Collectively, these results support the potential utility of UBE2A as a prognostic and diagnostic biomarker in selected malignancies, although its clinical applicability may vary depending on tumor type.

Somatic mutations affecting oncogenes and tumor suppressor genes are central drivers of malignant transformation and tumor evolution (63,64). Despite the overall mutation frequency of UBE2A across cancers being relatively low in the present analysis, a notable enrichment of UBE2A mutations was observed in mature B-cell neoplasms, whereby mutation rates were >10%. This tumor-type-specific pattern contrasts with the low prevalence of UBE2A alterations in the majority of solid tumors. These findings are consistent with previous reports suggesting that UBE2A mutations, while uncommon, may exert disproportionate functional effects in specific hematological malignancies (21,65). Such context-dependent mutational roles underscore the importance of considering tissue-specific molecular environments when interpreting the oncogenic importance of UBE2A alterations and warrant further functional investigation in hematologic cancer models.

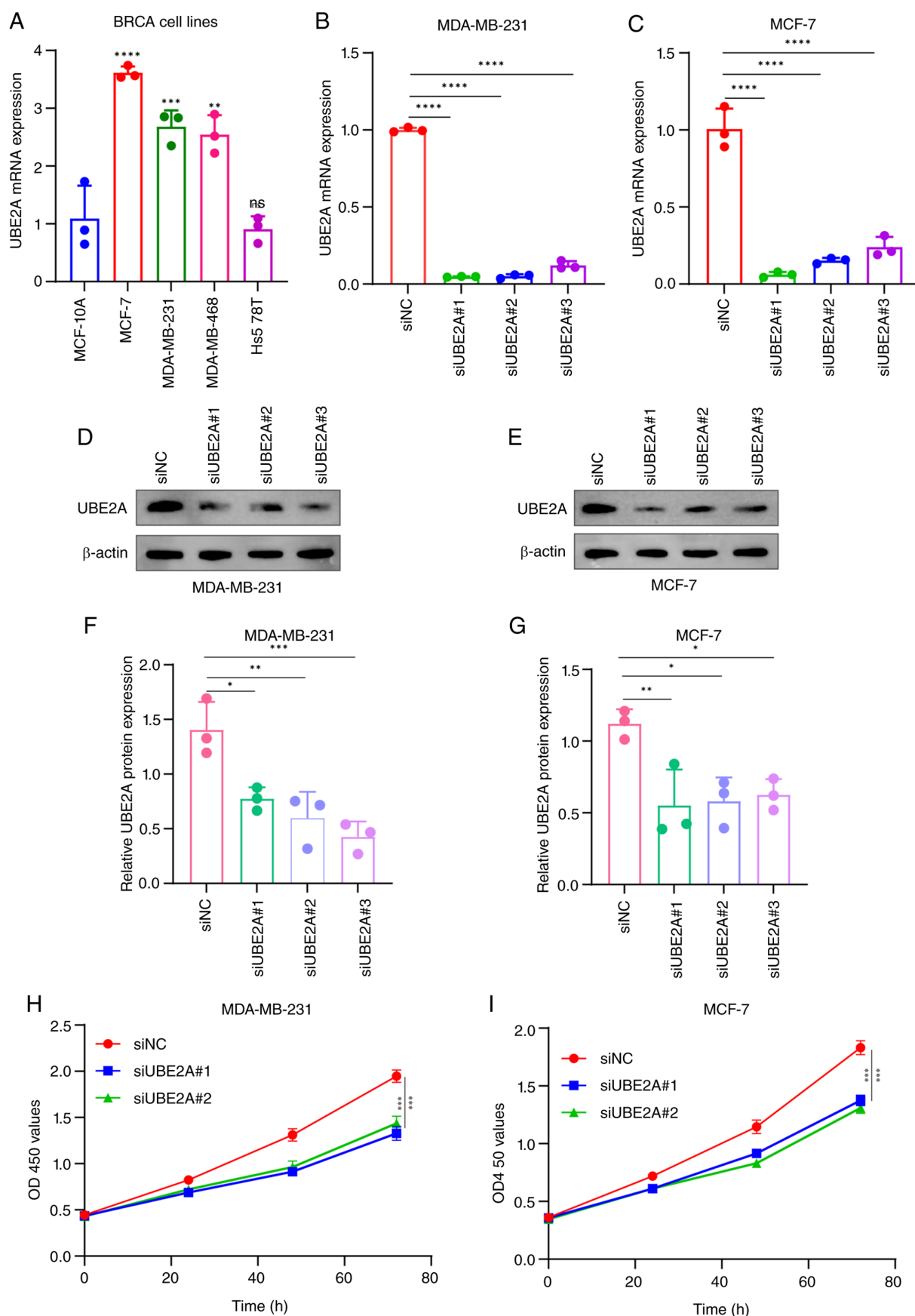


Figure 12. UBE2A expression in BRCA cell lines and validation of siRNA-mediated knockdown. (A) Relative UBE2A mRNA levels in BRCA cell lines and the normal breast epithelial cell line determined by qPCR. (B) qPCR analysis of UBE2A mRNA levels following transfection with three siRNAs in MDA-MB-231 cells. (C) qPCR analysis of UBE2A mRNA levels following transfection with three siRNAs in MCF-7 cells. (D-G) Western blotting assessment of UBE2A protein expression after siRNA transfection. (H and I) Cell Counting Kit-8 assays evaluating the effects of UBE2A knockdown on proliferation in MDA-MB-231 and MCF-7 cells. Statistical comparisons were performed relative to the siNC group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ and **** $P < 0.0001$. UBE2A, ubiquitin conjugating enzyme E2A; si, small interfering; NC, negative control; qPCR, quantitative PCR; OD450, optical density at 450 nm; ns, not significant.

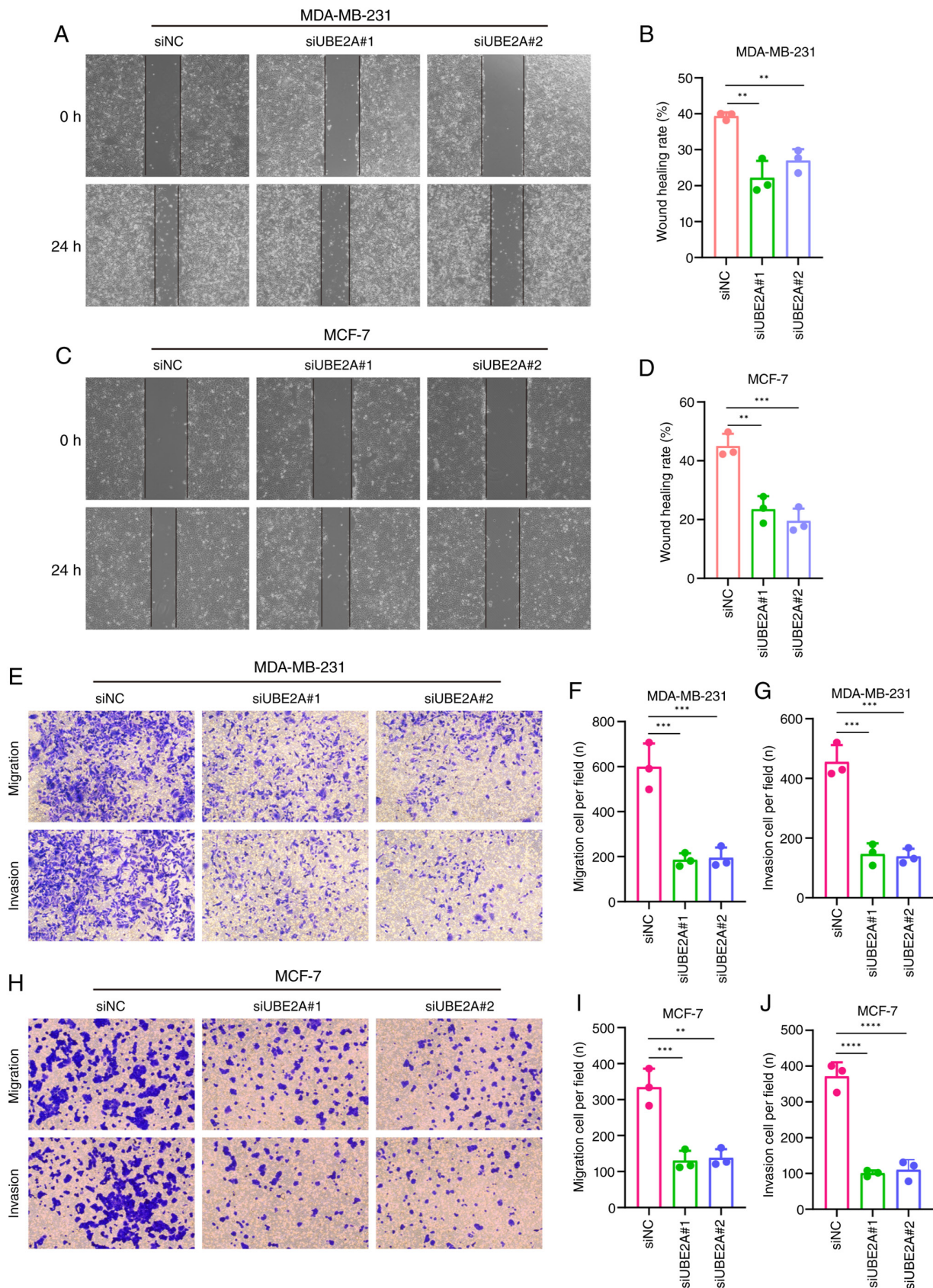


Figure 13. Effects of UBE2A knockdown on migration and invasion of BRCA cells. (A) Representative wound healing images of MDA-MB-231 cells following UBE2A knockdown. Magnification, x4. (B) Quantitative analysis of wound closure in MDA-MB-231 cells. (C) Representative wound healing images of MCF-7 cells following UBE2A knockdown. Magnification, x4. (D) Quantitative analysis of wound closure in MCF-7 cells. (E) Representative images of Transwell migration and invasion assays in MDA-MB-231 cells. Magnification, x10. (F) Quantification of migrated MDA-MB-231 cells. (G) Quantification of invaded MDA-MB-231 cells. (H) Representative images of Transwell migration and invasion assays in MCF-7 cells. Magnification, x10. (I) Quantification of migrated MCF-7 cells. (J) Quantification of invaded MCF-7 cells. Statistical comparisons were performed relative to the siNC group. Statistical comparisons were performed relative to the siNC group. **P<0.01, ***P<0.001 and ****P<0.0001. UBE2A, ubiquitin conjugating enzyme E2A; si, small interfering; NC, negative control.

The tumor microenvironment constitutes a highly dynamic network in which immune cells, stromal components and tumor cells interact to influence disease progression and therapeutic response (66,67). Increasing evidence has indicated that dysregulation of immune infiltration and immune signaling pathways contributes to immune evasion and resistance to therapy. In the present study, numerous immune infiltration algorithms were applied to minimize methodological bias and to comprehensively evaluate the association between UBE2A expression and immune cell composition across cancers. The present analyses revealed that higher UBE2A expression was frequently associated with increased infiltration of CD8⁺ T cells, dendritic cells, neutrophils and macrophage subsets in a number of tumor types. In addition, UBE2A expression correlated positively with numerous immune checkpoint and immunoregulatory genes, including IL-12A and CD276, which are known to modulate anti-tumor immunity and immune homeostasis within the tumor microenvironment (68). These associations suggest that UBE2A may participate in shaping immune-associated signaling networks, potentially contributing to an immunosuppressive or immune-dysregulated microenvironment that favors tumor progression. However, it should be noted that these observations were primarily derived from computational analyses of transcriptomic datasets and therefore do not establish a direct causal role for UBE2A in regulating anti-tumor immunity. Consequently, the immune-associated findings of the present study should be interpreted as hypothesis-generating evidence that requires further experimental validation. TMB and MSI have emerged as clinically relevant biomarkers for predicting responsiveness to immune checkpoint inhibitors (51,52). The observed correlations between UBE2A expression and both TMB and MSI across numerous cancer types raise the possibility that UBE2A expression may reflect underlying genomic instability and tumor immunogenicity, thereby providing complementary information for immunotherapy stratification.

Notably, single-cell transcriptomic analysis revealed relatively high UBE2A expression in proliferative T-cell populations within the tumor microenvironment. Proliferative T cells are generally considered an activated immune cell subset associated with ongoing anti-tumor immune responses, but persistent proliferative signaling may also reflect T-cell dysfunction or exhaustion under chronic tumor-associated immune stimulation (69). Therefore, the elevated expression of UBE2A in proliferative T cells suggests that UBE2A may participate in immune regulatory processes within the tumor microenvironment. Despite this, the present study did not directly investigate the biological function of UBE2A in T cells. Future studies employing immune-cell models, co-culture systems and immunocompetent animal models should aim to determine whether UBE2A directly influences T-cell activation, proliferation, exhaustion or anti-tumor immune responses. Although the present study primarily focused on the tumor-intrinsic functions of UBE2A in breast cancer cells, these findings suggest a potential immunomodulatory role of UBE2A that warrants further investigation through dedicated immune-associated functional experiments, such as T-cell co-culture systems and immune phenotype analyses.

Mechanistically, UBE2A has been reported to facilitate p53 degradation through the ubiquitin-proteasome

pathway (70) thereby attenuating p53-mediated cell cycle arrest and apoptotic signaling. Due to the central role of p53 in tumor suppression, dysregulation of this axis may represent a key mechanism through which UBE2A promotes malignant phenotypes. Beyond the p53 axis, the comparable suppressive phenotypes observed following UBE2A silencing in both wild-type p53 (MCF-7) and mutant p53 (MDA-MB-231) cells suggest that additional p53-independent mechanisms may be involved. As a ubiquitin-conjugating enzyme, UBE2A participates in ubiquitin-mediated protein turnover and may influence the stability of a number of proteins beyond p53, including heterochromatin protein 1 (HP1) and cyclin D1 (16,71).

The present enrichment analyses revealed significant associations between UBE2A and cell-cycle regulation, chromosome segregation, mitotic progression and proteasome-associated pathways. Consistent with these observations, previous studies have demonstrated that RAD6A (UBE2A) promotes homologous recombination-mediated DNA double-strand break repair through ubiquitin-dependent degradation of heterochromatin protein HP1 α , thereby facilitating chromatin remodeling and maintaining genome stability (71). In addition, RAD6A (UBE2A) has been reported to enhance DNA damage tolerance and repair signaling while inducing the expression of stemness-associated genes through histone H2B ubiquitination-mediated transcriptional regulation, ultimately contributing to tumor progression and acquired chemoresistance (18). These findings raise the possibility that UBE2A may facilitate tumor cell proliferation through the regulation of key cell-cycle regulators and mitotic proteins, thereby promoting G₁/S transition, maintaining mitotic fidelity and supporting efficient chromosome segregation during cell division. Dysregulation of these processes is a well-established driver of genomic instability and tumor progression (16,18,71). In addition, the enrichment of proteasome-associated pathways suggests that UBE2A may broadly regulate protein homeostasis through ubiquitin-dependent degradation mechanisms. Therefore, its oncogenic effects may not be restricted to p53 turnover but may also involve the modulation of additional cell-cycle, DNA repair or signaling proteins. Notably, antigen-processing pathways were also enriched among UBE2A-associated genes. Given that ubiquitin-mediated proteolysis serves a key role in generating peptides for MHC class I antigen presentation, aberrant UBE2A expression may influence tumor immune recognition and contribute to the immune-related associations observed in the present pan-cancer analyses. Collectively, these findings support a broader functional role of UBE2A beyond p53 regulation and suggest that both p53-dependent and p53-independent mechanisms may contribute to its tumor-promoting activities.

A previous study in hepatocellular carcinoma reported that UBE2A is regulated by an upstream non-coding RNA network and promotes tumor progression (22). Consistent with these observations, functional enrichment analyses of UBE2A co-expressed genes in the present study highlighted strong associations with cell cycle regulation and mitotic processes, as supported by GO and KEGG annotations. Notably, GSEA further revealed enrichment of antigen processing and presentation pathways, suggesting a potential association between UBE2A activity and tumor immunogenicity. Among the analyzed tumor types, BRCA was selected

for functional validation as UBE2A exhibited significant upregulation, strong diagnostic performance and unfavorable prognostic associations in BRCA within the pan-cancer analysis. Although the highest mutation frequency of UBE2A was observed in mature B-cell neoplasms and single-cell analyses demonstrated relatively high expression in proliferative T-cell populations, the primary objective of the present study was to evaluate the tumor-intrinsic role of UBE2A in a solid tumor model. Breast cancer was therefore selected as a representative cancer type with robust transcriptomic evidence and accessible experimental systems. Consequently, the potential functions of UBE2A in immune cells and hematological malignancies remain key topics for future investigations. In addition, single-cell transcriptomic analyses revealed distinct UBE2A expression patterns in the breast cancer tumor microenvironment, further supporting its potential biological relevance in BRCA progression. Complementing these bioinformatic findings, loss-of-function experiments demonstrated that UBE2A silencing significantly impaired the proliferative, migratory and invasive capacities of breast cancer cells *in vitro*. Collectively, these results indicate that UBE2A may contribute to tumor progression through coordinated regulation of cell cycle dynamics and immune-associated processes.

A number of limitations of the present study should be considered. First, although external validation was performed using independent GEO cohorts, the majority of pan-cancer analyses were still based on publicly available datasets and may therefore be influenced by dataset-specific biases. Additional validation using larger prospective clinical cohorts is warranted. Second, the associations identified between UBE2A expression and immune-associated characteristics were primarily derived from bioinformatic analyses and remain correlative in nature. Third, despite the enrichment of UBE2A expression in proliferative T-cell populations revealed by single-cell analyses, the experimental validation in the present study was restricted to breast cancer epithelial cells and direct evidence supporting an immunomodulatory role of UBE2A is currently lacking. Fourth, the functional experiments relied on transient siRNA-mediated knockdown, which may be associated with potential off-target effects. Future studies using stable gene modulation strategies, such as shRNA- or CRISPR/Cas9-mediated approaches, together with rescue experiments and immunocompetent animal models, are necessary to further validate the biological functions of UBE2A.

In conclusion, the present study provided a systematic pan-cancer evaluation of UBE2A, outlining its expression characteristics and clinical relevance across a broad range of malignancies. The results indicated that aberrant UBE2A expression was frequently associated with adverse clinical outcomes and displays measurable diagnostic and prognostic utility in selected cancer types. In addition, UBE2A expression showed consistent associations with immune cell infiltration patterns and the expression of immune regulatory molecules, suggesting its involvement in tumor-immune interactions. In breast cancer, UBE2A was significantly upregulated and correlated with unfavorable prognosis and functional assays further demonstrated that UBE2A depletion attenuated malignant phenotypes *in vitro*. Collectively, these findings supported a role for UBE2A in cancer progression

and suggested a potential association between UBE2A and immune-association processes, thereby underscoring the need for further mechanistic studies to clarify its biological functions and potential therapeutic value.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YW conceived and designed the study, performed bioinformatics analyses, conducted the cell experiments, collected and analyzed the data, generated the figures and visualizations, validated the experimental and computational results, and drafted the manuscript. PL supervised the study, provided research resources and technical support, participated in data interpretation, critically reviewed and revised the manuscript and managed the project. YW and PL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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