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Identification of DCAF11 as a Prognostic Biomarker in Clear Cell Renal Cell Carcinoma

Ferbian Milas Siswanto [1], Andrea Aprilia [2*], Maria Dara Novi Handayani [1], Ida Bagus Gde Rama Wisesa [3], Annabella Dominique Setiadi[4], Donna Sherlyn Gunawan[4]

[1] Department of Biochemistry, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Penjaringan, Jkt Utara, Jakarta, 14440, Indonesia,
[2] Department of Clinical Pathology, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Penjaringan, Jkt Utara, Jakarta, 14440, Indonesia,
[3] Faculty of Veterinary Medicine, Brawijaya University, Puncak Dieng Eksklusif, Kalisongo, Dau, Malang, 65151, Indonesia,
[4] Bachelor of Medicine Study Programme, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Penjaringan, Jkt Utara, Jakarta, 14440, Indonesia,

* Corresponding author: andrea.aprilia@atmajaya.ac.id

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Abstract: Clear cell renal cell carcinoma (ccRCC) is the most common and lethal subtype of renal cell carcinoma and exhibits pronounced molecular heterogeneity that limits the prognostic accuracy of conventional clinicopathological parameters. DDB1 and CUL4 associated factor 11 (DCAF11) is a substrate receptor of the CUL4-based E3 ubiquitin ligase complex that regulates cell cycle progression, genome stability, and stress-responsive signaling; however, its clinical relevance in ccRCC remains poorly understood. In this study, we systematically investigated the expression pattern, prognostic significance, immune relevance, and molecular networks associated with DCAF11 in ccRCC using integrative bioinformatics analyses. Transcriptomic and clinical data from The Cancer

Genome Atlas (TCGA) and normal tissue references were analyzed, with independent validation performed using multiple GEO datasets. Our results demonstrate that DCAF11 is significantly dysregulated in ccRCC and that its expression varies across pathological stages. Reduced DCAF11 expression is associated with unfavorable clinical outcomes and correlates with genes involved in mismatch repair, DNA methylation, and immune cell infiltration. Functional enrichment and network analyses revealed that DCAF11-associated gene signatures are enriched in pathways related to cell cycle regulation, DNA replication, ubiquitin-mediated proteolysis, and immune-related signaling. Collectively, these findings identify DCAF11 as a prognostic biomarker in ccRCC and suggest that it may contribute to tumor progression through coordinated regulation of genomic stability and tumor–immune interactions.

Keywords: DDB1 and CUL4 associated factor 11 (DCAF11); clear cell renal cell carcinoma; prognostic biomarker; bioinformatics analysis; signaling pathways.

DCAF11作为透明细胞肾细胞癌预后生物标志物的鉴定

摘要：透明细胞肾细胞癌（clear cell renal cell carcinoma，ccRCC）是肾细胞癌中最常见且致死率最高的亚型，具有显著的分子异质性，从而限制了传统临床病理参数的预后评估准确性。DDB1和CUL4相关因子11（DCAF11）是基于CUL4的E3泛素连接酶复合体的底物受体，参与调控细胞周期进程、基因组稳定性以及应激反应信号通路；然而，其在ccRCC中的临床意义仍未得到充分阐明。本研究采用整合生物信息学分析方法，系统评估了DCAF11在ccRCC中的表达模式、预后价值、免疫相关性及其分子调控网络。通过分析癌症基因组图谱（The Cancer Genome Atlas，TCGA）数据库及正常组织参考数据，并结合多个基因表达综合数据库（Gene Expression Omnibus，GEO）数据集进行独立验证。研究结果表明，DCAF11在ccRCC中呈显著表达失调，且其表达水平在不同病理分期中存在差异。DCAF11表达降低与不良临床预后相关，并与错配修复、DNA甲基化及免疫细胞浸润相关基因呈显著相关。功能富集及网络分析显示，与DCAF11相关的基因特征显著富集于细胞周期调控、DNA复制、泛素介导的蛋白质降解及免疫相关信号通路。综上所述，本研究鉴定DCAF11为ccRCC的潜在预后生物标志物，并提示其可能通过协同调控基因组稳定性及肿瘤–免疫相互作用促进肿瘤进展。

关键词：DDB1 和 CUL4 相关因子 11（DCAF11）；透明细胞肾细胞癌；预后生物标志物；生物信息学分析；信号通路

1. Introduction

Cancer remains the second leading cause of death worldwide, posing a major challenge to public health and modern medicine [1]. Among its complications, metastasis remains its deadliest feature driving the lowest survival rates, despite the approval of more than 200 anticancer drugs over the past six decades. This poor outcome largely arises from the diverse interactions between cancer cells and their surrounding microenvironment, which vary across patients and tumor types. Traditional bulk sequencing approaches, although widely applied, often obscure the intratumoral heterogeneity that underlies these complex interactions [2]. In contrast, targeted therapies have demonstrated improved clinical outcomes by addressing patient-specific molecular alterations. With the rapid advancement of bioinformatics and molecular technologies, cancer can now be detected at earlier stages, and key regulatory genes can be identified, offering novel opportunities to design more effective therapeutic strategies [3].

Among the candidate genes, a poorly studied component of E3 ligase called DDB1- and CUL4-associated factor 11 (DCAF11), has emerged as an important player in maintaining cellular homeostasis. To date, there is an extremely limited study on DCAF11 and its biological function. DCAF11 targets various proteins involved in diverse pathways for degradation via ubiquitination, including Holliday junction resolvase GEN-1 [4], p21 [5], stem-loop binding protein (SLBP) [6], tripartite motif-containing 28 (TRIM28) or KRAB-

associated protein 1 (KAP1) [7], centromeric protein A (CENP-A) or PRKAR1B [8], and NRF2 [9]. NRF2 is a transcription factor that protects cells from oxidative stress and reactive oxygen species (ROS) [10]. While NRF2 is mainly controlled by the CRL3–Keap1 complex, DCAF11 serves as a crucial backup regulator, especially under non-homeostatic conditions [11]. When DCAF11 is downregulated or lost, NRF2 becomes hyperactivated, allowing cancer cells to thrive [12,13]. Beyond NRF2 regulation, DCAF11 also mediates targeted protein degradation, such as binding and degrading the oncogenic protein BRD4, thereby suppressing tumor growth [14]. Its absence disrupts cell-cycle control through stabilization of SLBP, leading to uncontrolled histone synthesis and pro-inflammatory cytotoxicity [6]. Collectively, these findings suggest that reduced DCAF11 expression critically contributes to tumor development [15].

Although emerging evidence has begun to elucidate the biological functions of DCAF11, its precise role in cancer progression remains incompletely understood, underscoring the need for further investigation. Advances in bioinformatics and the availability of large-scale public cancer datasets provide valuable opportunities to explore molecular alterations associated with tumor development and progression across diverse malignancies [16,17]. These approaches facilitate the identification of candidate biomarkers and potential therapeutic targets. In this context, we performed a comprehensive analysis of DCAF11, including its expression patterns, prognostic significance, genetic alterations, methylation status, immune associations, and functional networks. Using integrative analyses of The Cancer Genome Atlas (TCGA) and independent validation datasets, we identified a significant association between DCAF11 expression and patient survival in kidney renal clear cell carcinoma (KIRC). Furthermore, DCAF11 expression was associated with molecular features linked to disease aggressiveness. Collectively, our findings suggest that DCAF11 may serve as a potential biomarker for ccRCC, warranting further investigation in experimental and clinical settings.

2. Materials and Methods

2.1. Data selection and *DCAF11* expression profiles

The transcript levels of DCAF11 in tumor, adjacent normal controls and corresponding clinical information were obtained from The Cancer Genome Atlas (TCGA) via GDC Data Portal (https://portal.gdc.cancer.gov/). Gene expression data were analyzed in the form of normalized transcript per million (TPM) values, and log2 transformation [log2(TPM+1)] was applied for downstream analyses. The expression of DCAF11 in normal tissues were obtained from Genotype-Tissue Expression (GTEx) project. To minimize technical variability and ensure comparability between datasets, expression analyses involving TCGA and GTEx data were conducted using established web-based platforms, including Tumor Immune Estimation Resource 2.0 (TIMER 2.0, https://compbio.cn/timer2/) and the University of Alabama at Birmingham Cancer Data Analysis Portal (UALCAN, https://ualcan.path.uab.edu/), which implement standardized preprocessing and normalization pipelines. Expression differences across pathological stages, as well as patient demographic variables (race, gender, and age), were analyzed using TCGA-KIRC data via UALCAN and visualized as box plots.

For external validation, three independent microarray datasets (GSE53757, GSE151419, and GSE117890) were retrieved from the Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/). Raw or processed GEO data were subjected to standard preprocessing procedures, including background correction and quantile normalization, followed by log2 transformation where applicable. Analyses of GEO datasets were performed independently to avoid cross-platform bias.

Protein expression levels of DCAF11 between primary tumors and matched normal tissues were compared using data from the Clinical Proteomic Tumor Analysis Consortium (CPTAC), accessed via the UALCAN. Immunohistochemistry (IHC) images of DCAF11 in normal and tumor tissues were obtained from the Human Protein Atlas (HPA, https://www.proteinatlas.org/) database for qualitative validation.

To reduce the impact of batch effects, analyses were primarily conducted within individual datasets or using harmonized platforms that incorporate batch correction. Cross-dataset comparisons were interpreted cautiously and supported by consistent findings across independent cohorts. A schematic overview of the study design is presented in Fig. 1.

2.2. Genetic alteration analysis of *DCAF11*

Genetic alterations of DCAF11 were explored using the cBioPortal platform (https://www.cbioportal.org/). The gene was searched within the TCGA Pan-Cancer Atlas Studies using the “Quick Select” option. Information on mutation frequency, copy number alterations, and mutation types across different TCGA cancer cohorts was retrieved from the Types Summary section. In addition, three-dimensional structural models were used to visualize the locations of DCAF11 mutations.

2.3. Survival prognosis analysis of DCAF11 in KIRC

The prognostic value of DCAF11 in clear cell renal cell carcinoma (TCGA-KIRC) was evaluated using the Gene Expression Profiling Interactive Analysis 2 (GEPIA2, http://gepia2.cancer-pku.cn/#survival)

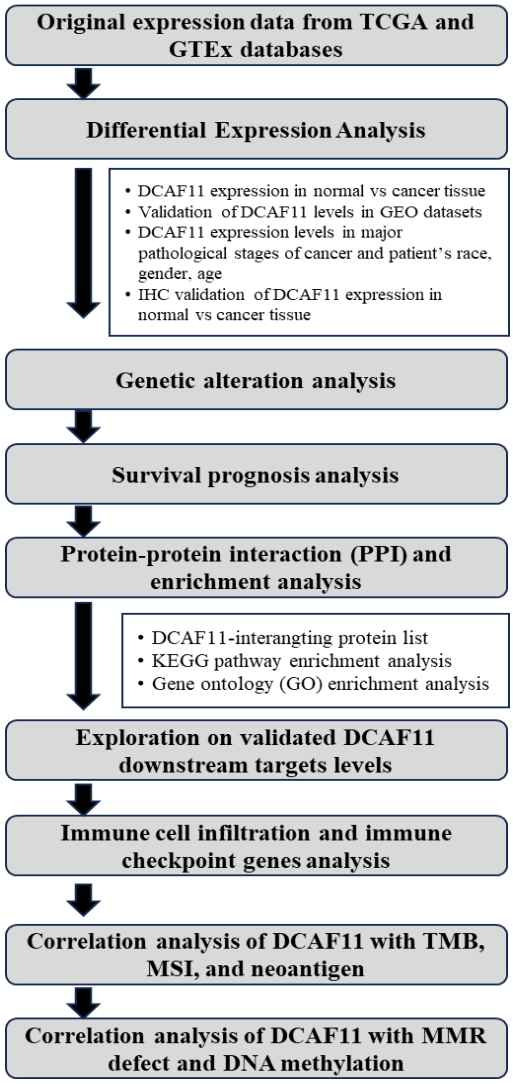

Figure 1. Flowchart of this study

platform. Overall survival (OS) and disease-free survival (DFS) analyses were performed using the 'Survival Analysis' module. Patients were stratified into high- and low-DCAF11 expression groups based on the median expression value (50% cutoff). Kaplan–Meier survival curves were generated to compare OS and DFS between groups, and differences between groups were assessed using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported, and p-values < 0.05 were considered statistically significant.

2.4. Protein–protein interaction network (PPI) and enrichment analysis

To explore the molecular functions and signaling pathways associated with DCAF11, protein–protein interaction (PPI) networks were constructed using the STRING database (https://string-db.org/), with Homo sapiens specified as the organism. The top 50 DCAF11-interacting proteins were retrieved based on experimentally supported and high-confidence interactions. A minimum interaction confidence threshold was applied, and protein pairs with significant co-expression were identified. To further expand and validate the interaction landscape, we used the ZS Revelen (https://revelen.zsservices.com/) network analysis tool. Functional enrichment analyses were subsequently performed to investigate the biological relevance of DCAF11-associated genes. Gene Ontology (GO) terms, including biological processes, molecular functions, and cellular components, as well as Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses, were conducted using the ShinyGO (version 0.85.1, https://bioinformatics.sdstate.edu/go/) and were visualized using the SRplot (https://www.bioinformatics.com.cn/en).

2.5. Exploration of DCAF11 downstream targets

To further elucidate the functional role of DCAF11 in ccRCC, several validated downstream targets, including NRF2, KAP1 (TRIM28), CDKN1A (p21), CENPA, and SLBP, were systematically examined. Protein expression profiles of these targets were obtained from the CPTAC dataset via the UALCAN platform. In addition, correlation analyses were performed to evaluate the relationships between DCAF11 protein abundance and the protein levels of its downstream substrates. Protein-level analyses were prioritized over transcriptomic data in this section because DCAF11 functions as a substrate receptor of the CRL4 E3 ubiquitin ligase complex, primarily regulating protein stability and turnover through post-translational ubiquitination mechanisms rather than directly modulating gene transcription. Therefore, assessing protein expression and protein–protein correlations provide a more biologically relevant insight into DCAF11-mediated regulatory effects in ccRCC.

2.6. Analysis of tumor-infiltrating immune cells (TIICs)

The relationship between DCAF11 expression and tumor immune infiltration was assessed using TIMER 2.0 and CIBERSORTx web portal (http://cibersortx.stanford.edu/), which deconvolute bulk transcriptomic data to estimate immune cell composition. Three immune-related scores (ImmuneScore, StromalScore, and ESTIMATEScore) were calculated using the ESTIMATE R package to evaluate the tumor microenvironment (TME). The ESTIMATEScore, representing overall tumor purity, was correlated with DCAF11 expression. Associations between DCAF11 expression, immune cell infiltration, and immune checkpoint genes were evaluated using Spearman's correlation, with scatter plots used for visualization.

2.7. Correlation of DCAF11 expression with TMB and MSI

Tumor mutational burden (TMB) and microsatellite instability (MSI) are established biomarkers for predicting responses to immune checkpoint inhibitor

therapy. In this study, somatic mutation data for TCGA-KIRC patients were obtained from the GDC portal to calculate TMB and MSI scores. The associations between DCAF11 expression and TMB as well as MSI were subsequently evaluated using Spearman's correlation analysis to explore the immunogenomic relevance of DCAF11 in clear cell renal cell carcinoma.

2.8. Correlation of DCAF11 with mismatch repair (MMR) and DNA methylation

To explore genetic instability, correlations between DCAF11 expression and five mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2, and EPCAM) were evaluated using Spearman's correlation. Additionally, correlations with DNA methylation–related genes (DNMT1, DNMT3A, DNMT3B, and TET1) were analyzed. Scatter plots were generated to visualize significant associations.

2.9. Statistical analysis

Two-group comparisons were performed using Student's t-test. Survival analyses used Kaplan–Meier curves, log-rank tests, and Cox proportional hazard regression models. Spearman's correlation coefficients were calculated for correlation analyses. Unless otherwise specified, $p < 0.05$ was considered statistically significant.

3. Results

3.1. DCAF11 is significantly dysregulated in ccRCC

To determine whether DCAF11 expression is altered in human malignancies, we compared its transcript levels between tumor and adjacent normal tissues using TCGA data (Fig. 2A) or normal tissue references from GTEx (Fig. S1). DCAF11 expression differed significantly between tumor and adjacent normal samples, indicating marked transcriptional dysregulation in ccRCC. Consistent results were obtained when tumor tissues were compared with matched adjacent normal tissues, confirming that the observed alteration was not dependent on the choice of normal reference. To assess the reproducibility of our findings, DCAF11 expression was validated in multiple independent GEO datasets, including GSE53757, GSE151419, and GSE117890. Across all datasets, DCAF11 exhibited consistent differential expression patterns between ccRCC and normal kidney tissues, despite differences in sample size and experimental platforms (Fig. 2B). Reduced expression of DCAF11 was likely due to an elevated level of its promoter methylation (Fig. S2).

Considering that proteins serve as the direct mediators of biological function, we further examined DCAF11 protein expression using immunohistochemistry data from the HPA database and protein expression data from CPTAC. Consistent with the transcriptomic findings, DCAF11 protein levels were substantially lower in ccRCC tissues compared with normal renal tissues (Fig. 2C), supporting the reliability of the expression analysis at both mRNA and protein levels.

3.2. Association between DCAF11 expression and clinicopathological features of ccRCC

We next evaluated the relationship between DCAF11 expression and clinicopathological characteristics. DCAF11 expression varied significantly across pathological stages (Fig. S3A), with a trend toward lower expression in more advanced stages, suggesting a potential association with disease progression. In contrast, minimal differences in DCAF11 expression were observed among patients stratified by race (Fig. S3B), sex (Fig. S3C), or age (Fig. S3D), suggesting that DCAF11 expression is largely independent of demographic characteristics and may reflect intrinsic tumor biology rather than population-specific factors.

3.3. Mutation analysis of DCAF11 in ccRCC

Based on cBioPortal data, we analyzed the genetic alteration profile of DCAF11 in ccRCC and observed a low overall alteration frequency (0.78% of 511 cases), predominantly driven by point mutations rather than copy number amplifications (Fig. S4A). Missense mutations represented the major alteration type (Fig. S4B), with both missense and truncating mutations dispersed across the DCAF11 coding region, indicating the absence of a dominant mutational hotspot. Structural modeling further demonstrated that these altered residues were spatially distributed throughout the predicted three-dimensional structure of the DCAF11 (Fig. S4C), suggesting that genetic alterations are unlikely to be the primary mechanism driving its dysregulation in ccRCC.

3.4. Prognostic Value of DCAF11 in ccRCC

We next investigated the prognostic significance of DCAF11 expression in TCGA-KIRC datasets. Kaplan–Meier survival analysis demonstrated that patients with low DCAF11 expression exhibited significantly poorer overall survival (OS) compared with those with high expression ($P < 0.05$; Fig. 3A). A similar trend was observed for disease-free survival (DFS) (Fig. 3B). These findings indicate that reduced DCAF11 expression is associated with unfavorable clinical outcomes, supporting its potential role as a protective or tumor-suppressive factor in ccRCC.

3.5. Functional enrichment and pathway analysis of DCAF11-associated genes

To gain mechanistic insight into the biological processes associated with DCAF11 in ccRCC, we performed Gene Ontology (GO) and KEGG pathway analyses of the top DCAF11-coexpressed genes, and

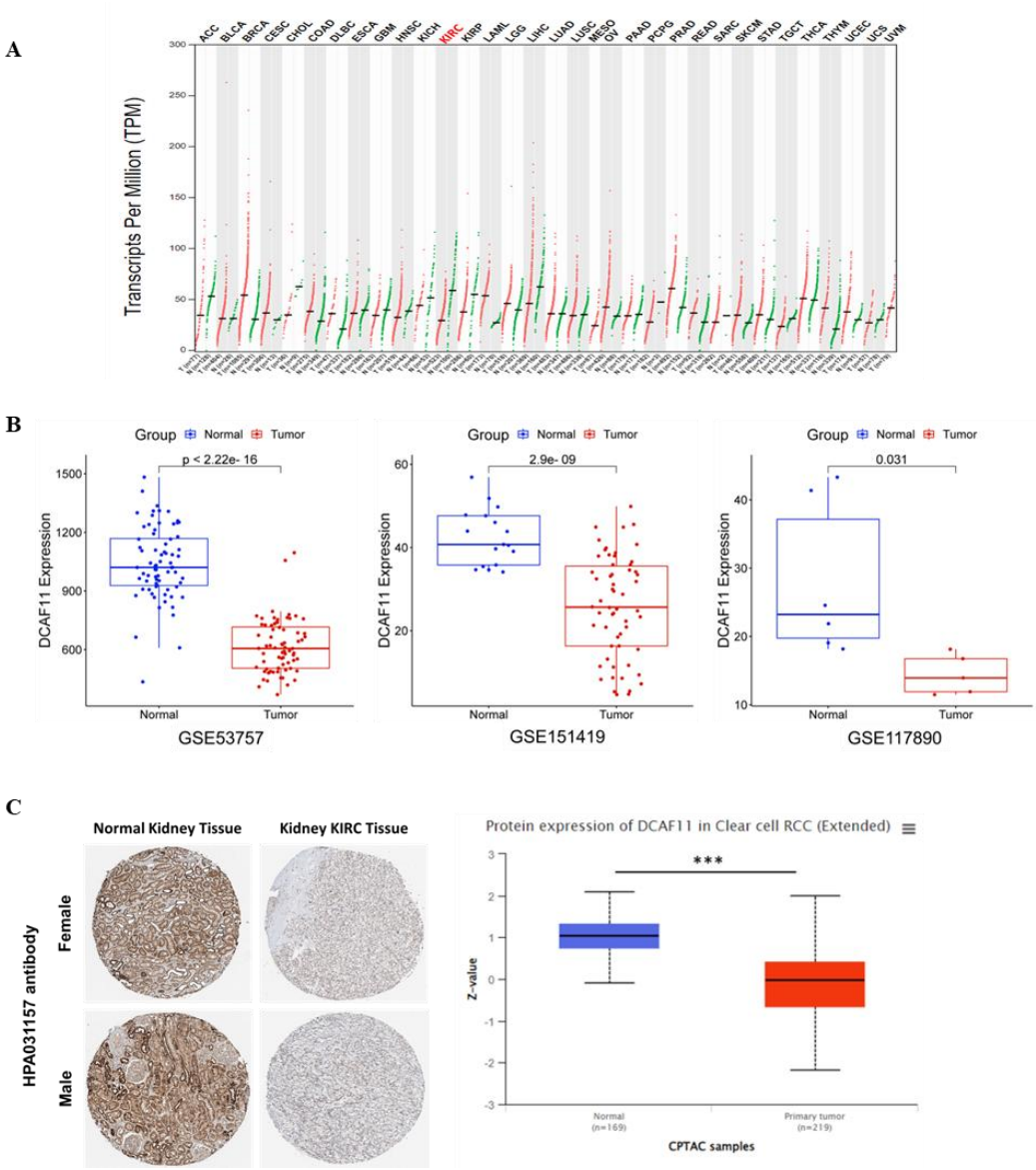

Figure 2. Differential Expression of DCAF11 in ccRCC. (A) The transcript data of DCAF11 in various tumors or tumor subtypes in the TIMER database. (B) Validation of DCAF11 expression status in the three GEO datasets. (C) Comparison of DCAF11 protein expression between tumor and healthy samples (right) and IHC images in normal and cancer tissues (left).

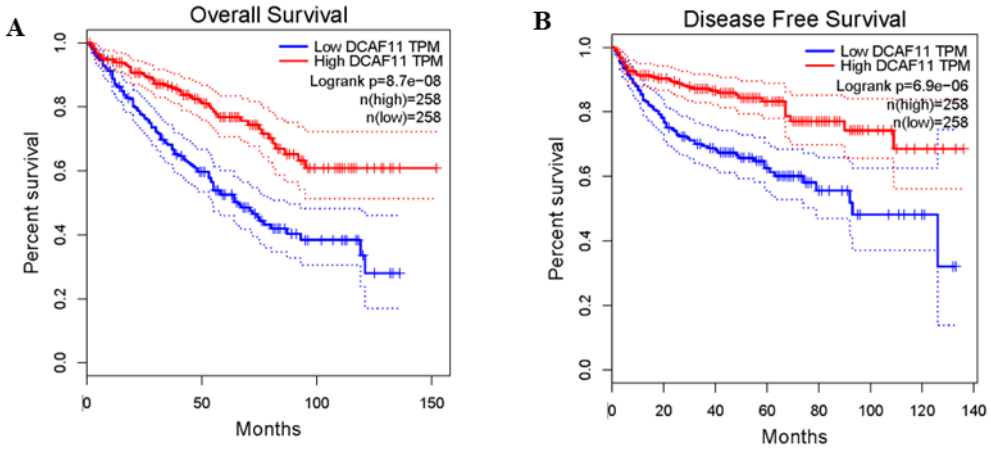

Figure 3. Kaplan–Meier Survival Curves of High and Low Expression of DCAF11 in ccRCC. (A) Overall Survival and (B) Disease Free Survival.

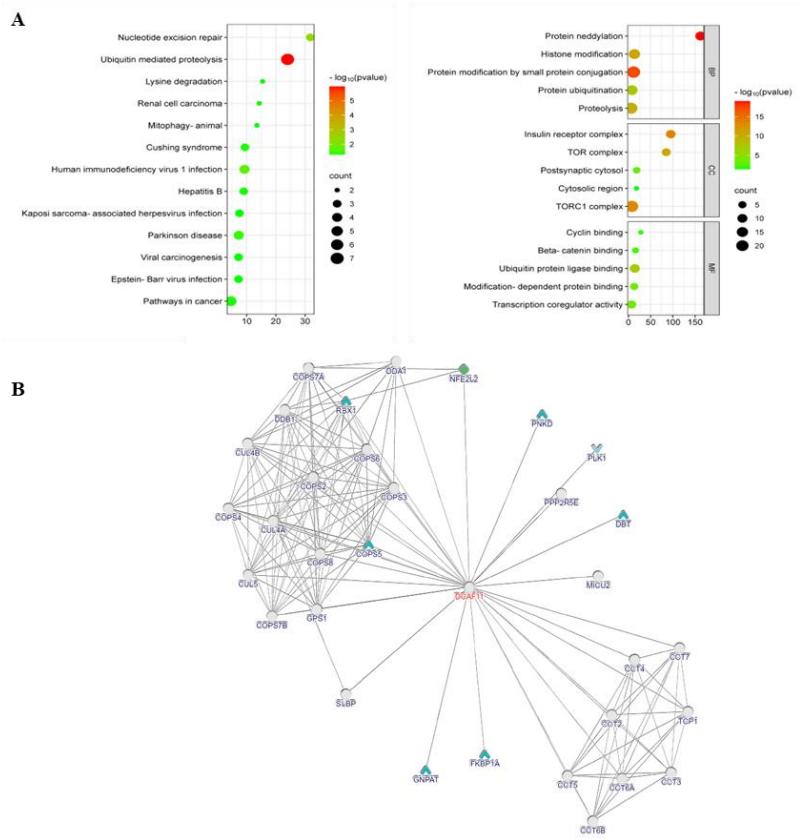

Figure 4. DCAF11-Related Gene Enrichment Analysis. (A) KEGG pathway (left) and GO enrichment (right) analysis of DCAF11 and co-expressed genes. (B) Experimentally validated DCAF11 binding protein were mapped in PPI network.

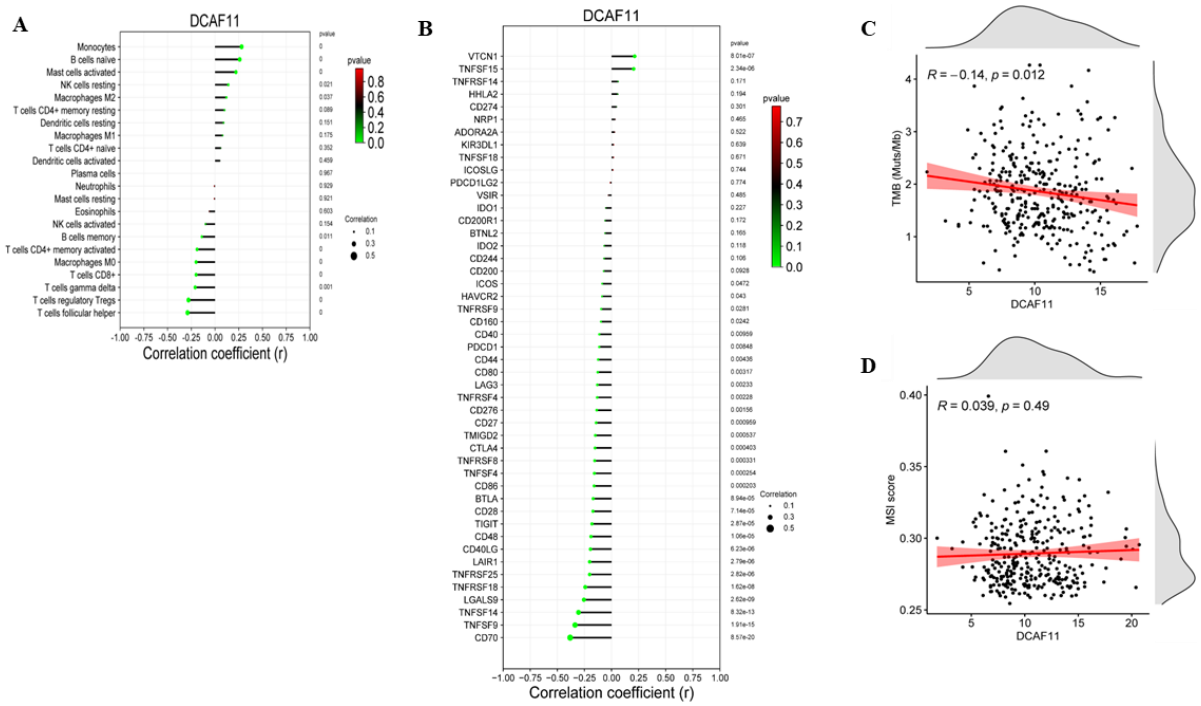

Figure 5. The connection between DCAF11 expression levels and (A) infiltration level of immune cells, (B) immune checkpoint genes, (C) TMB, and (D) MSI in ccRCC from TCGA-KIRC database.

constructed a protein network. Enrichment and pathway analyses revealed that DCAF11-associated genes were significantly enriched in pathways related to cell cycle regulation, DNA replication, ubiquitin-mediated proteolysis, and immune-related signaling (Fig. 4A). Protein–protein interaction network analysis further identified interconnected modules and hub genes associated with these pathways (Fig. 4B), indicating that DCAF11 may play a central role in coordinating cell proliferation, genomic stability, and immune-related processes in ccRCC.

3.6. DCAF11 is associated with its downstream targets in ccRCC

Analysis of the CPTAC proteomics dataset demonstrated that almost all DCAF11-target proteins was significantly elevated in ccRCC tumors, except for NRF2 (Fig. S5A-E). In ccRCC samples, DCAF11 was inversely correlated with all validated downstream targets. Specifically, DCAF11 protein levels showed negative correlations with NRF2, p21, SLBP, and CENPA (PRKAR1B), consistent with its role as a substrate receptor in the CRL4 E3 ubiquitin ligase complex. KAP1 (TRIM28) also displayed a negative association with DCAF11 protein abundance (Fig. S5F-J). Collectively, these protein-level relationships support a model in which DCAF11 overexpression contributes to ccRCC progression through post-translational destabilization of key regulators of cell-cycle control, chromatin integrity, and redox homeostasis.

3.7. Correlation of DCAF11 with the TIICs, TMB and MSI

We further explored the relationship between DCAF11 expression and immune cell infiltration. DCAF11 expression was significantly correlated with the abundance of several immune cell populations ($P < 0.05$, Fig. 5A), indicating that DCAF11 may be linked to the immune landscape of ccRCC tumors. Additionally, analysis revealed that DCAF11 was significantly co-expressed with the majority of immune-related genes ($P < 0.05$, Fig. 5B). Notably, most immune checkpoint genes exhibited negative correlations with DCAF11 expression in ccRCC, suggesting a potential involvement of DCAF11 in immune regulatory networks across cancers.

TMB and MSI serve as robust immunogenomic markers predictive of therapeutic responsiveness to immune checkpoint inhibition in various cancers. Elevated DCAF11 expression showed a negative correlation with TMB ($p = 0.012$, Fig. 5C), but not MSI ($p > 0.05$, Fig. 5D), indicating that DCAF11-high tumors tend to exhibit a low-mutational profile. These findings suggest a potential role for DCAF11 in shaping immune escape mechanisms independent of hypermutation status.

3.8. DCAF11 correlates with MMR and DNA methylation–related genes

Given the role of genomic instability in ccRCC, we investigated the relationship between DCAF11 expression and genes involved in mismatch repair (MMR). DCAF11 expression showed significant correlations with multiple MMR-related genes ($P < 0.05$, Fig. 6A-E), particularly MSH2, MSH6, and EPCAM, suggesting a close association with DNA repair machinery. In parallel, DCAF11 expression showed significant correlations with DNMT3A and DNMT3B ($P < 0.05$, Fig. 6A-E). These findings suggest that DCAF11 may participate in ccRCC progression through coordinated regulation of DNA repair and epigenetic modification, contributing to genomic stability and transcriptional reprogramming in cancer.

4. Discussion

Clear cell renal cell carcinoma (ccRCC) exhibits profound molecular heterogeneity [18], undermining the prognostic utility of traditional clinicopathological factors and necessitating robust biomarkers for risk stratification. In this study, we systematically investigated the clinical and biological significance of DCAF11 in ccRCC using an integrative bioinformatics framework. Our results demonstrate that DCAF11 is aberrantly expressed at both transcriptomic and proteomic levels in ccRCC, exhibits stage-associated expression patterns, and is linked to patient survival and unfavorable biological features, including genomic instability, epigenetic regulation, and immune microenvironment remodeling. Using both TCGA and GEO cohorts support the robustness of the observed associations across independent datasets. Importantly, the variation of DCAF11 expression across pathological stages suggests that its dysregulation may reflect dynamic changes associated with tumor progression rather than an early static alteration. This dynamic expression pattern strengthens the prognostic relevance of DCAF11 and supports its potential utility in patient stratification.

Importantly, although genetic alterations of DCAF11 were rare in ccRCC, its expression showed marked transcriptional and proteomic dysregulation. This finding suggests that aberrant DCAF11 activity in ccRCC is unlikely to be driven by mutational events but rather by transcriptional regulation or post-transcriptional mechanisms, a phenomenon frequently observed for E3 ligase adaptors in cancer [19]. The absence of dominant mutational hotspots further supports the concept that DCAF11 contributes to tumor progression primarily through altered regulatory activity rather than structural disruption.

DCAF11, also known as WDR23, functions as a substrate receptor for the CUL4–DDB1 E3 ubiquitin ligase complex and plays a critical role in proteostasis by targeting specific proteins for ubiquitin-mediated degradation. Our observation that DCAF11 expression

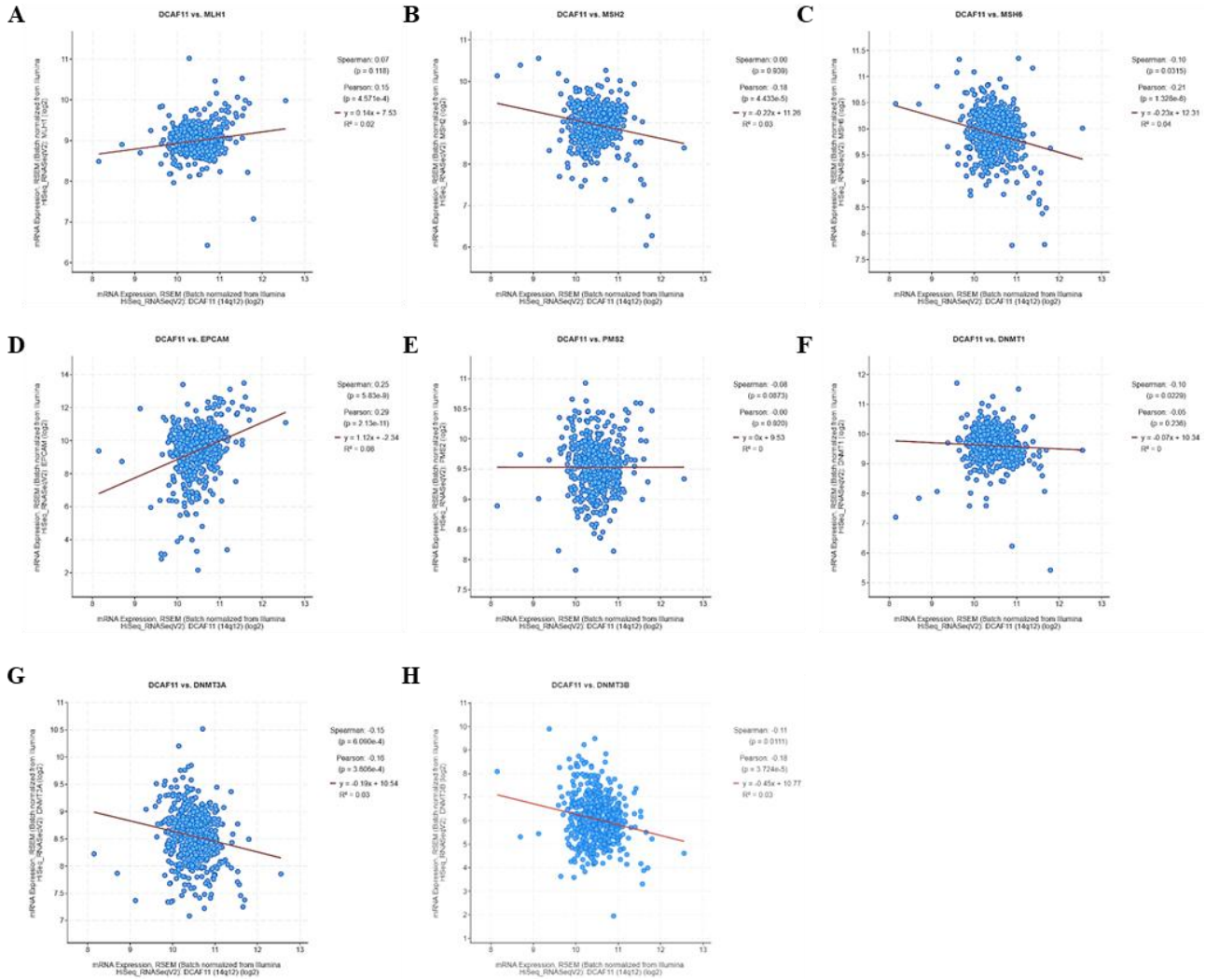

Figure 6. The connection between DCAF11 expression levels and five well-identified MMR genes, including (A) MLH-1, (B) MSH2, (C) MSH6, (D) EPCAM, (E) PMS2, as well as three DNA methyltransferases genes such as (F) DNMT1, (G) DNMT3A, and (H) DNMT3B.

is significantly altered in ccRCC is consistent with the growing recognition that dysregulation of ubiquitin–proteasome pathways is a hallmark of renal carcinogenesis [20]. The dysregulated expression pattern of DCAF11 in ccRCC resembles that reported for well-established biomarkers such as IGF2BP3 [21], with progression-linked patterns. Mechanistically, previous studies have shown that $CRL4^{DCAF11}$ targets proteins such as p21 for S-phase degradation [5], SLBP for histone supply [6], and CENPA [8], which are involved in cell cycle regulation and DNA replication. In addition, DCAF11 has been reported to regulate NRF2 degradation independently of KEAP1, thereby influencing cellular redox homeostasis [9,23]. In the context of ccRCC, where hypoxia and oxidative stress are prominent features, alterations in DCAF11 expression may be associated with dysregulated stress-response pathways [24] and metabolic adaptation [25]. However, these interpretations remain speculative and require further experimental validation.

The association observed in our study between DCAF11 expression and MMR genes suggests that DCAF11 dysregulation may occur in concert with altered DNA repair capacity, which is a hallmark of ccRCC [26], thereby influencing tumor evolution and therapeutic resistance. These results parallel the role of CUL4A/B E3 ligase roles in DNA damage response and tumorigenesis [27]. Such coordination between proteostasis and DNA repair pathways may enable tumor cells to tolerate replicative stress while maintaining sufficient genomic plasticity to support disease progression [28]. The significant correlation between DCAF11 expression and MMR genes, together with its association with low TMB status, suggests that reduced DCAF11 expression may be linked to impaired genomic maintenance and altered immune surveillance mechanisms, rather than a hypermutated phenotype.

In addition to genomic stability, our findings highlight a potential link between DCAF11 and epigenetic regulation. The significant correlations between DCAF11 expression and DNA methylation–related genes suggest that DCAF11 expression may be associated with epigenetic regulatory processes,

although the underlying mechanisms remain to be elucidated. Studies showed that ccRCC exhibits global hypomethylation and promoter hypermethylation, driving metabolic shifts and resistance [29], but DCAF11 links remain associative via prognostic signatures rather than mechanistic. Given the involvement of CUL4-based ligases in chromatin-associated processes [30], it is plausible that DCAF11 participates indirectly in shaping the epigenetic state of ccRCC cells, thereby influencing gene expression programs relevant to tumor progression.

Beyond intrinsic tumor biology, our study highlights a significant link between DCAF11 and the immune microenvironment of ccRCC. We observed robust correlations between DCAF11 expression and tumor--infiltrating immune cells, as well as widespread associations with immune-related genes. Notably, DCAF11 expression was negatively correlated with most immune checkpoint genes and TMB. While the precise mechanisms underlying this association remain to be elucidated, DCAF11-mediated regulation of cell cycle and stress-response pathways may indirectly influence immune recognition or immune cell recruitment. ccRCC is considered an immunogenic tumor and responds favorably to immune checkpoint inhibitors [31]. These findings suggest that reduced DCAF11 expression in ccRCC may be associated with an altered immune microenvironment, potentially contributing to immune dysregulation or impaired anti-tumor immunity, resembling patterns observed for other components of the ubiquitin–proteasome system, although it does not appear to be directly linked to neoantigen load or immune checkpoint inhibitor resistance based on current biomarkers [29,32]. Collectively, these observations position DCAF11 as a biomarker that integrates tumor-intrinsic and tumor-extrinsic features, an increasingly important consideration in precision oncology.

Clinically, our survival analyses demonstrate that reduced DCAF11 expression is associated with significantly poorer overall and disease-free survival in ccRCC, and that DCAF11 serves as an independent prognostic factor. This tumor-specific prognostic relevance distinguishes DCAF11 from many pan-cancer biomarkers and underscores its potential utility in ccRCC risk stratification. From a translational perspective, integrating DCAF11 expression into existing prognostic models may improve patient stratification, particularly in identifying individuals at higher risk of progression who may benefit from intensified surveillance or combination therapies.

Several limitations of this study should be acknowledged. First, the analyses were based primarily on retrospective public datasets, and prospective clinical validation will be required to confirm the prognostic utility of DCAF11. Second, although we identified significant associations between DCAF11 expression and multiple biological processes, causality cannot be inferred from bioinformatics analyses alone. Experimental studies are needed to elucidate the precise molecular mechanisms by which DCAF11 contributes to ccRCC progression and immune modulation. Finally, the impact of DCAF11 on therapeutic response, particularly to immunotherapy or targeted agents, warrants further investigation.

5. Conclusion

In conclusion, our study identifies DCAF11 as a central regulator of proteostasis, cell-cycle progression, redox balance, and immune modulation in ccRCC, with significant prognostic and therapeutic implications. Incorporation of DCAF11 into risk stratification frameworks may refine prognostic accuracy beyond existing clinical models and open new avenues for ubiquitin–proteasome–based precision oncology in renal cancer.

Declarations

Author Contributions

Conceptualization, F.M.S.; methodology, F.M.S.; validation, A.A., M.D.N.H., and I.B.G.R.W.; formal analysis, F.M.S.; investigation, F.M.S., and A.A.; data curation, F.M.S.; writing—original draft preparation, F.M.S., A.D.S., and D.S.G.; writing—review and editing, A.A., M.D.N.H., and I.B.G.R.W.; visualization, F.M.S.; supervision, A.A.; project administration, F.M.S. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data is contained within the article or supplementary material: The data presented in this study are available in https://jonuns.com/index.php/journal.

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The author declares that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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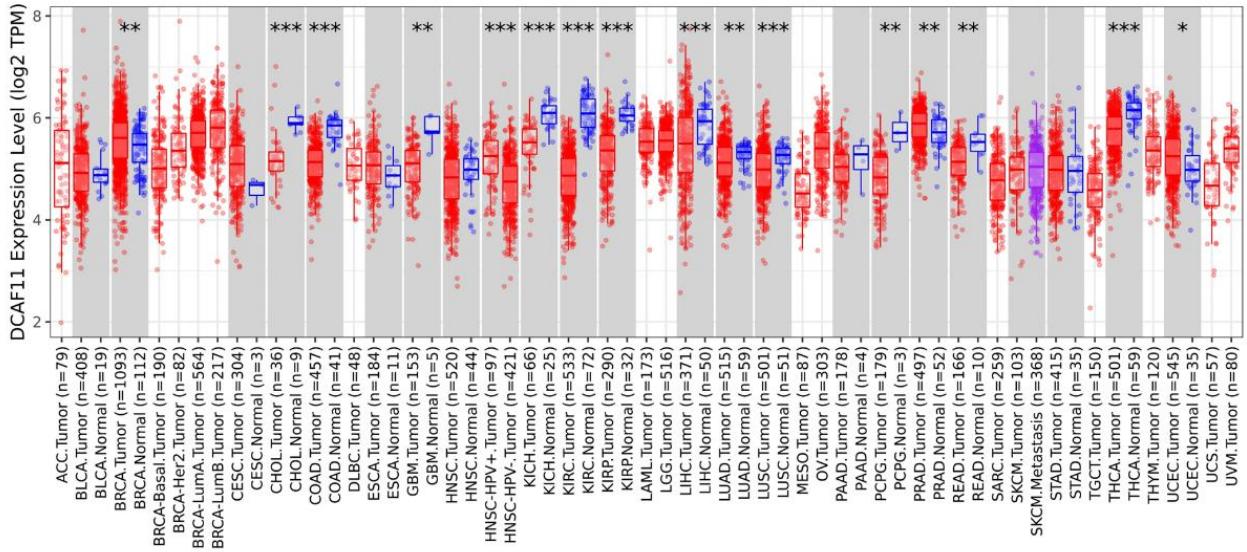
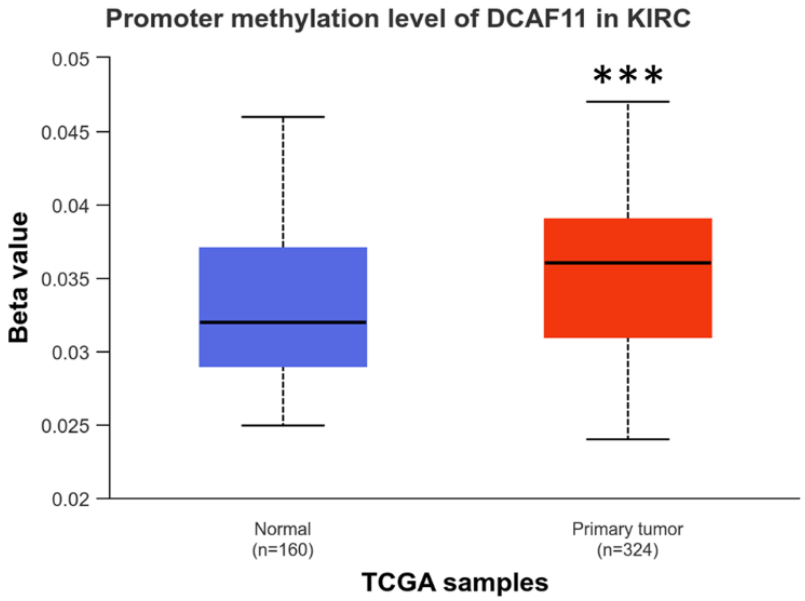
Supplementary Files

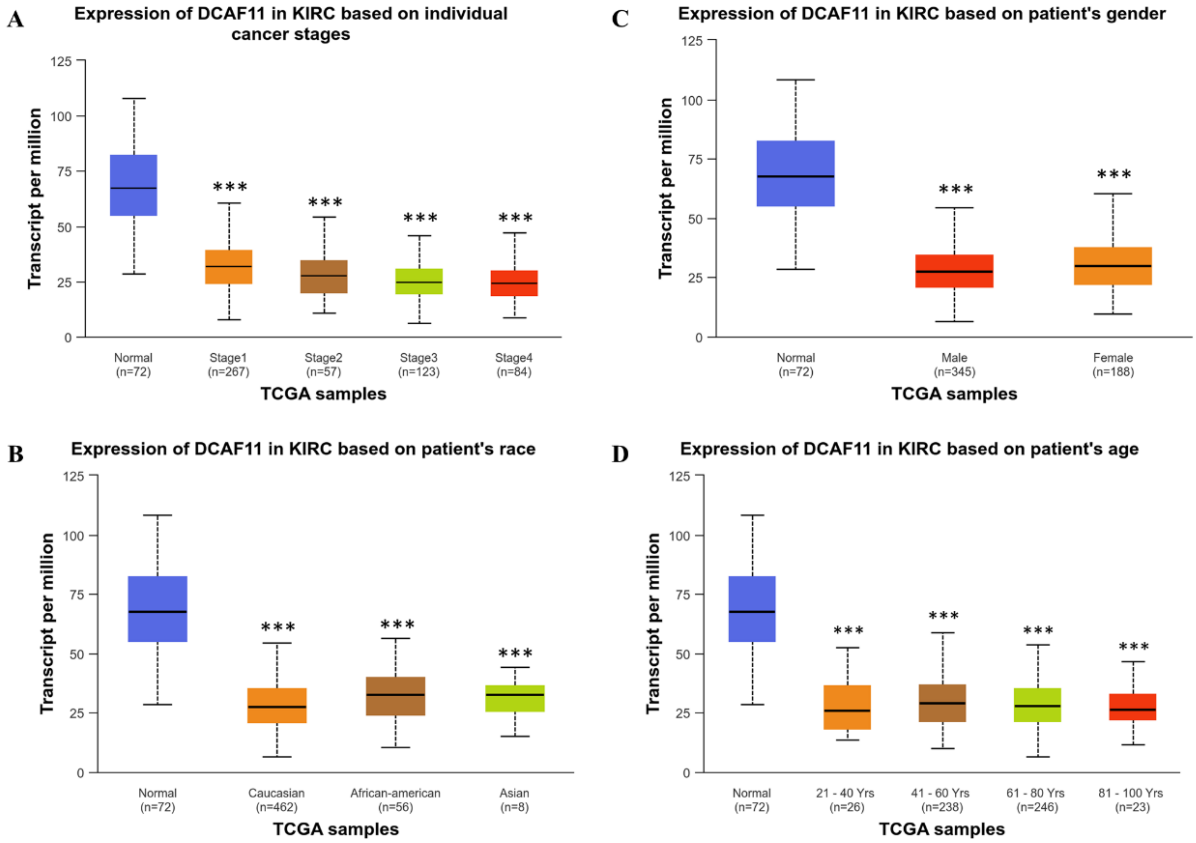
Supplementary Figure 1



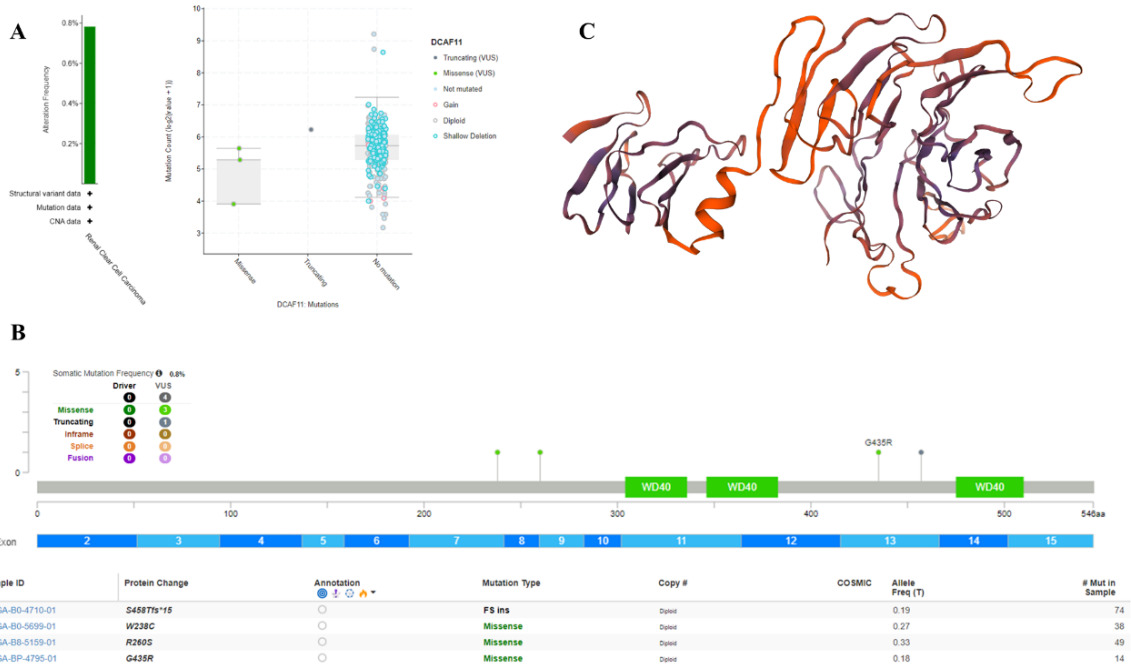
Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4



Sample ID	Protein Change	Annotation	Mutation Type	Copy #	COSMIC	Allele Freq (T)	# Mut in Sample
TCGA-B0-4710-01	*S458Tfs*15*		FS ins	Diploid		0.19	74
TCGA-B0-5699-01	*W238C*		Missense	Diploid		0.27	38
TCGA-B8-5159-01	*R260S*		Missense	Diploid		0.33	49
TCGA-BP-4795-01	*G435R*		Missense	Diploid		0.18	14

Supplementary Figure 5