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COMPREHENSIVE ANALYSIS OF PDZD2 EXPRESSION AND REGULATORY MECHANISMS IN BREAST INVASIVE CARCINOMA: IMPLICATIONS FOR PROGNOSIS AND THERAPEUTIC TARGETING

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Abstract

The investigation focused on elucidating the role of PDZD2 expression and its regulatory mechanisms in Breast Invasive Carcinoma (BRCA). Employing the UALCAN database, PDZD2 expression analysis unveiled a significant down-regulation in cancerous cells compared to normal controls, suggesting its involvement in BRCA proliferation. Further dissecting PDZD2 expression across various parameters revealed consistent down-regulation in different cancer stages, racial groups, genders, and age categories within BRCA patients, indicative of its pivotal role in disease progression. Additionally, this study explored the promoter methylation status of PDZD2, revealing a significant divergence between BRCA samples and normal controls. Analyzing promoter methylation across different parameters uncovered dynamic variations, with distinct methylation patterns observed across cancer stages, racial groups, genders, and age groups. Survival analysis using the KM plotter tool demonstrated a significant correlation between PDZD2 expression levels and overall survival in BRCA patients, with low PDZD2 expression correlating with higher survival rates. Furthermore, mutational analysis using the cBioPortal platform revealed a mutation rate of 4% in BRCA samples, predominantly featuring amplifications, deep deletions, and some missense

mutations in PDZD2. However, these genetic alterations were observed to have minimal impact on PDZD2 dysregulation in BRCA. Collectively, these findings emphasize the multifaceted involvement of PDZD2 in BRCA pathogenesis, emphasizing its potential as a prognostic biomarker and therapeutic target in BRCA management.

Keywords: Breast Invasive Carcinoma; Diagnosis: Treatment

1. Introduction:

Cancer is a serious health problem and is second leading cause of deaths worldwide. Globally 1 of 6 deaths is because of cancer (1-5). Breast invasive carcinoma (BRCA) is common cause of cancer death in women after lung cancer (6). There were about 2.2 million BRCA in 2020 and is expected to increase up to 3 million by 2040 (7-9). While both inherent and intrinsic risk factors like genetic, sex, ethnicity, age, metabolic, therapies hormonal lifestyle and diet are linked with BRCA (10, 11). BRCA can be controlled by early diagnosis, avoiding risk factor and enhancing treatment (12). However, BRCA treatment is challenging due to long-term recurrence, metastasis and drug resistance, inherent heterogeneity and functional features of tumor varies patient to patient (5, 13, 14).

PDZD2 (PDZ domain containing 2) is a protein coding gene and its coded protein is contains six PDZ domains localizes to the endoplasmic reticulum. PDZ domain containing 2 (PDZD2) also cited as (KIAA0300, PIN-1, PAPIN) activated in prostate cancer (AIPC). While PDZ domain-containing protein 3 (PDZK3)}, which is a six-PDZ (for PSD95, Discs-large and ZO-1) domain protein (15). PDZD2 is expressed in multiple mammalian tissues but highly expressed in cancer tissues (16, 17). PDZD2 have been reported to suppress tumor but its mechanism is inexplicable (18). Even in acute myeloid leukemia (AML) PDZD2 combining with secreted PDZD2 functions as tumor suppressor (19). Some reports elucidated that PDZD2 induce quiescence of BRCA with transcriptional activation of p53 (18, 20). Some findings showed the high-level amplification of PDZD2 in breast phyllodes tumors (9, 21). However, best to our knowledge, the role of PZDZ2 in BRCA has not been yet elucidate through Bioinformatics.

In the current study, different bioinformatics methods are used to analyze expression level and prognostic significance of PDZD2 in BRCA. The Cancer Genome Atlas (TCGA) database, Kaplan-Meier database and UALCAN platforms were used to conduct this research.

2. Material and methods

2.1 Expression analysis of PDZD2 in BRCA

UALCAN is user friendly database and is quiet helpful in analyzing cancer data (22). We analyze PDZD2 expression in normal samples and BRCA samples by analyzing data from TCGA platform. We also analyze expression based on different parameters as patient's age, patient's gender, patient's age and patient's race by utilizing UALCAN database.

2.2 Promoter methylation analysis of PDZD2

The data related to RNA expression, DNA methylation, viral infection, and clinical features of the cancer patients are present UALCAN database (16). For the analysis of promotor methylation level of PDZD2 in BRCA we used UCALAN database. Moreover, we also analyzed promoter methylation data of PDZD2 in different clinical parameters, such as patient's age, patient's gender, patient's age and patient's race.

2.3 Survival analysis of PDZD2

We used Kaplan Meier (KM) plotter to analyze the impact of PDZD2 on overall survival (OS) of BRCA patients. The best available tool to examine survival durations in cancer patients (23, 24). KM plotter is user friendly platform and researchers use it to investigate prognostic value of a gene

of interest. This platform is extensively used to measure the impact of specific gene on OS of cancer patients.

2.4 Mutational analysis of PDZD2

cBioPortal is a genomic database which enables researchers to examine genetic alterations across different cancers (25). cBioPortal is easy to go and key database for genomic research (25, 26). In the present study, we used this database to perform mutational analysis of PDZD2 in BRCA patients.

3. Results

3.1 Expression Analysis of PDZD2 in BRCA and normal control Samples

Our primary focus was directed towards analyzing the expression of PDZD2 in samples from both breast invasive carcinoma (BRCA) patients and normal controls, utilizing the UALCAN database (Figure 1). Our comprehensive analysis revealed a notable down-regulation of PDZD2 expression in cancerous cells compared to normal controls. This significant down-regulation suggests a potential association between PDZD2 expression and the proliferation of BRCA cells. These findings shed light on the intricate molecular mechanisms underlying BRCA progression, implicating PDZD2 as a potential regulator in the pathogenesis of this disease.

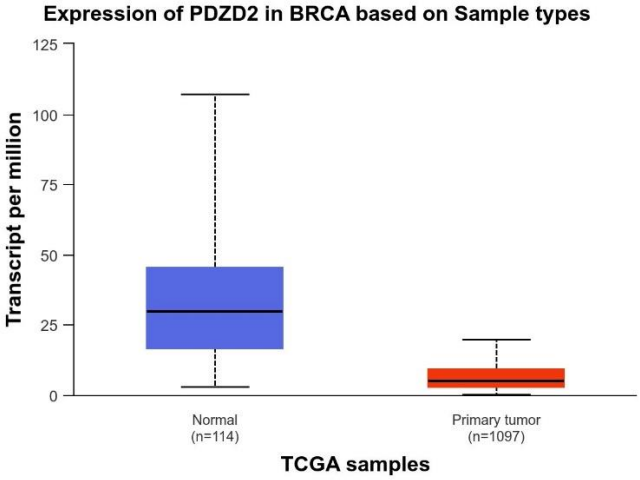

Figure 1: Expression pattern of PZDZ2 in BRCA and control samples. P-value < 0.05.

3.2 Expression analysis of PDZD2 in BRCA samples divided based on different parameters:

Concurrently, we conducted an analysis of PDZD2 expression in BRCA samples across various clinical parameters, including individual cancer stages, patient's race, gender, and age (Figure 2). Initially, we evaluated PDZD2 expression across different cancer stages and observed a significant down-regulation of PDZD2 in BRCA across all stages compared to normal samples (Figure 2A). Subsequently, we investigated PDZD2 expression in BRCA patients of diverse racial backgrounds, revealing consistent down-regulation of PDZD2 across different racial groups relative to normal samples (Figure 2B). Furthermore, we examined PDZD2 expression in BRCA patients stratified by gender, which indicated significant down-regulation of PDZD2 in both male and female patients compared to normal samples (Figure 2C). Finally, we explored the association between PDZD2 expression and patient age in BRCA. Our analysis unveiled down-regulation of PDZD2 expression across various age groups among BRCA patients, further underscoring the potential significance of PDZD2 in the context of age-related changes in BRCA pathology.

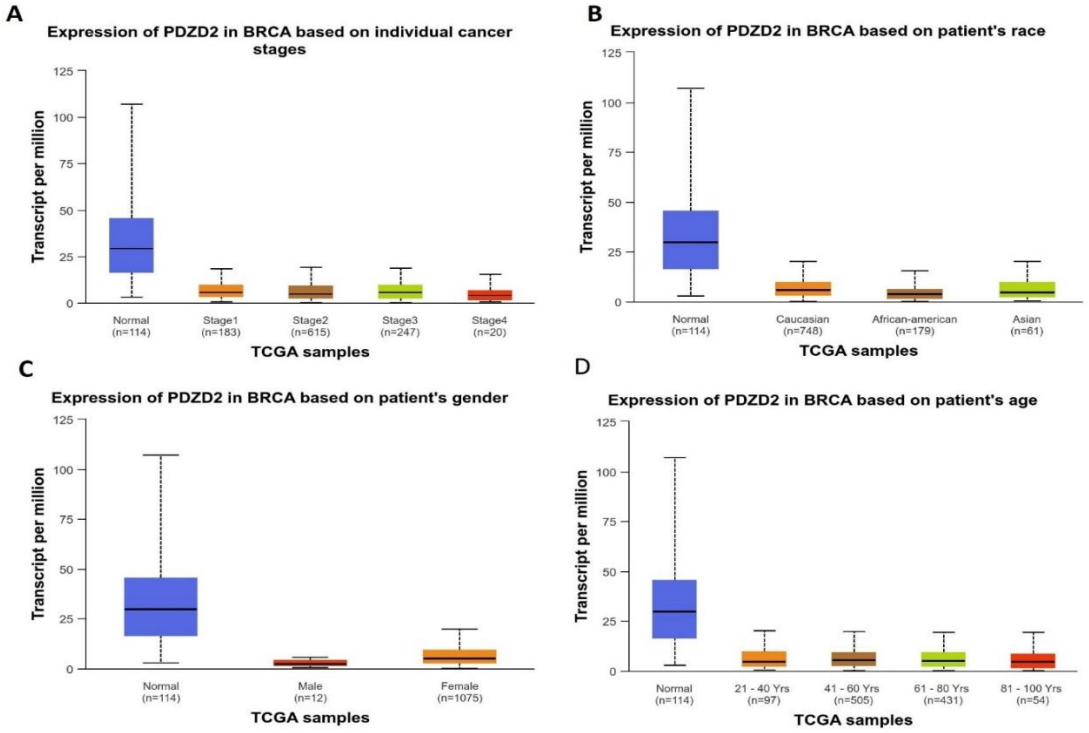

Figure 2: PDZD2 expression across different clinical variables of BRCA. P-value < 0.05.

3.3 Promoter methylation of PDZD2 in BRCA and normal control samples

Multiple studies underscore the role of promoter methylation in regulating gene expression (27, 28). Hence, we investigated the divergence in promoter methylation of PDZD2 in BRCA samples and normal control samples using the UALCAN database (Figure 3). Our analysis revealed significant variation, specifically hypomethylation, in the promoter methylation status of PDZD2 in BRCA compared to normal control samples (Figure 3). This observation suggests potential epigenetic dysregulation of PDZD2, highlighting its involvement in BRCA pathogenesis. Such findings contribute to our understanding of the molecular mechanisms underlying BRCA development and offer insights into the role of PDZD2 as a potential biomarker or therapeutic target in BRCA management.

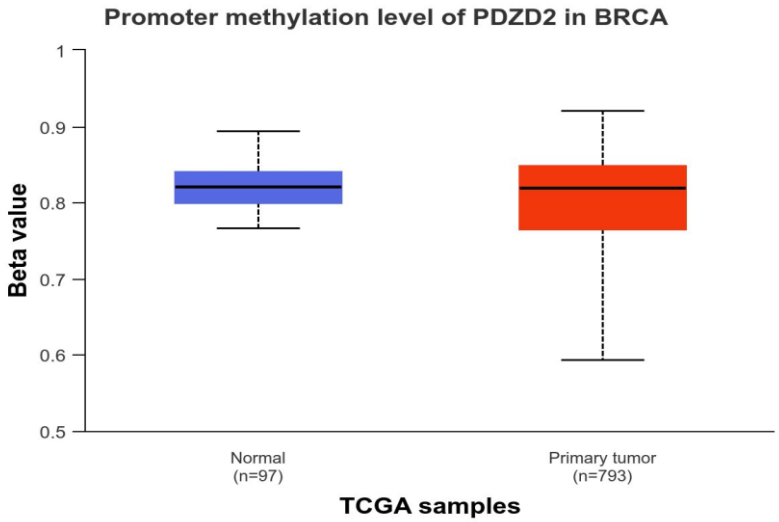

Figure 3: Promoter methylaytion pattern of PDZD2 in BRCA and control samples.

3.4 Promoter methylation of PDZD2 in BRCA samples divided based on different parameters:

We explored various parameters to analyze the promoter methylation of PDZD2 in BRCA) (Figure 4. Initially, we scrutinized PDZD2 promoter methylation across different BRCA stages relative to normal samples. Our findings revealed variation among stages, with the first three stages exhibiting hypermethylation and the fourth stage showing hypomethylation (Figure 4A). Subsequently, we investigated PDZD2 promoter methylation based on the race of BRCA patients. Interestingly, we observed hypomethylation in PDZD2 promoter regions across races except in Caucasians, where hypermethylation was prominent (Figure 4B). Moreover, analysis of PDZD2 promoter methylation according to patient gender unveiled gender-specific variations, with females exhibiting hypermethylation and males showing hypomethylation (Figure 4C). Furthermore, we explored PDZD2 promoter methylation concerning patient age, revealing varying methylation levels across different age groups (Figure 4D). These comprehensive analyses underscore the intricate relationship between PDZD2 promoter methylation and diverse clinical parameters in BRCA, shedding light on the multifaceted mechanisms underlying PDZD2 expression regulation in BRCA pathogenesis.

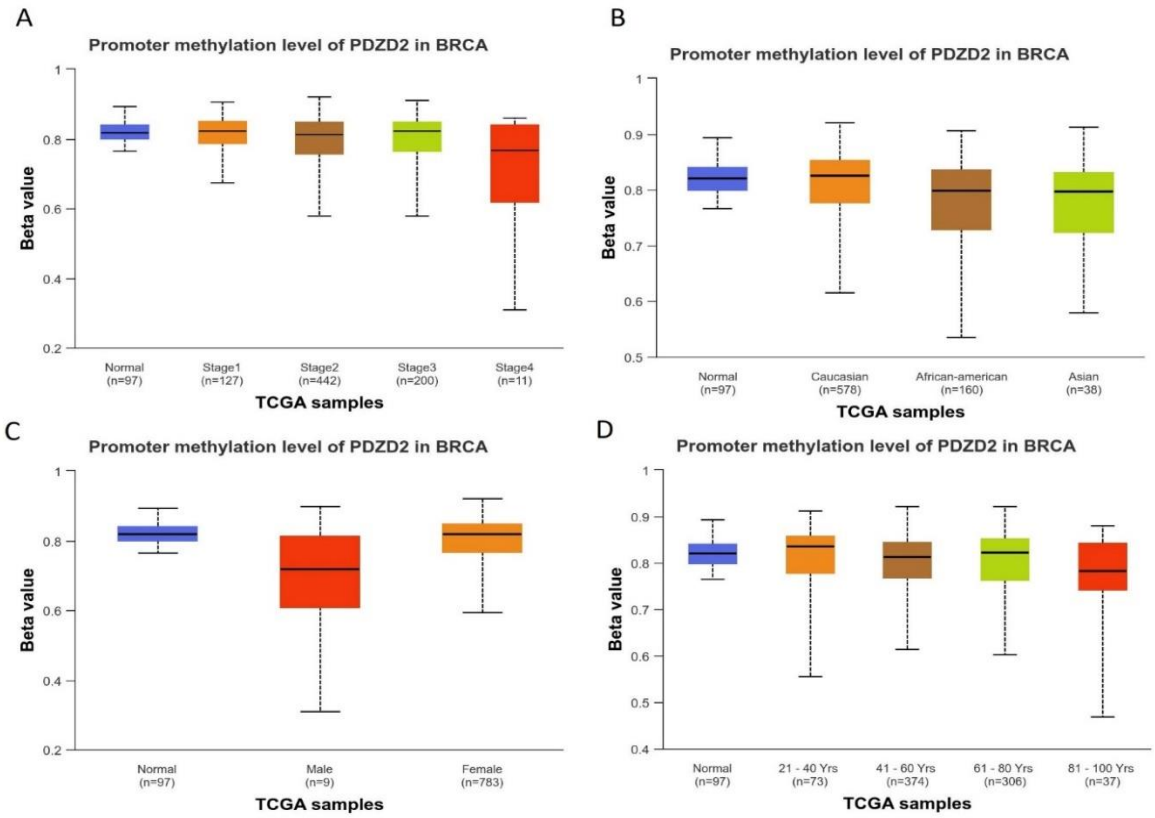

Figure 4: PDZD2 promoter methylation pattern across different clinical variables of BRCA. P-value < 0.05.

3.5 Survival analysis of PDZD2

Employing the KM plotter tool, we conducted an analysis to assess the overall survival (OS) of patients in relation to PDZD2 gene expression in breast BRCA. Our investigation revealed a significant correlation between PDZD2 expression levels and patient survival outcomes. Specifically, BRCA patients exhibiting low PDZD2 expression demonstrated notably higher OS rates compared to those with high PDZD2 expression (Figure 5). These findings underscore the pivotal role of PDZD2 in influencing the survival outcomes of BRCA patients, emphasizing its potential clinical significance as a prognostic marker in BRCA management.

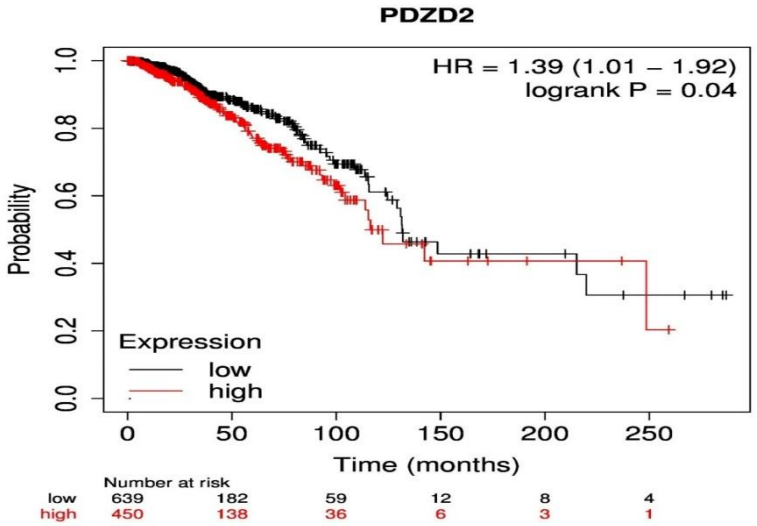

Figure 5: KM survival curve of PZDZ2 in BRCA patients. P-value < 0.05.

3.6 Mutational analysis of PDZD2 in BRCA

Utilizing the cBioPortal platform, we conducted a comprehensive mutational analysis of PDZD2 in BRCA. Our investigation revealed a mutation rate of 4% in BRCA samples. The observed genetic alterations in PDZD2 included amplifications, deep deletions, and several missense mutations (Figure 6). Despite the presence of genetic variations, our analysis suggested that these alterations had minimal impact on the dysregulation of PDZD2 in BRCA. These findings contribute to our understanding of the genetic landscape of PDZD2 in BRCA and highlight the need for further exploration to elucidate its functional implications in the disease.

Figure 6: Oncoplot of PDZD2 mutations in BRCA samples**.**

4. Discussion

Our investigation into PDZD2 expression patterns in BRCA and normal controls unveiled a significant down-regulation of PDZD2 in cancerous cells compared to normal controls. This finding implies a potential association between PDZD2 expression and BRCA proliferation, suggesting PDZD2 as a putative regulator in BRCA pathogenesis.

In colorectal cancer, PDZD2 down-regulation has been observed, correlating with tumor aggressiveness and poor prognosis (29, 30). Similarly, in ovarian cancer, reduced PDZD2 expression has been associated with advanced disease stages and worse patient outcomes (31, 32). Furthermore, in prostate cancer, PDZD2 alterations have been linked to disease progression and metastasis (18).

Furthermore, the intricate involvement of PDZD2 in cancer development extends beyond its expression levels. Epigenetic modifications, such as promoter methylation, are reported to modulate PDZD2 expression, influencing tumor behavior (33). Additionally, genetic alterations, including mutations and copy number variations, can also significantly disrupt PDZD2 expression in cancer development (34). However, our study revealed that neither epigenetic nor genetic alterations significantly contribute to the dysregulation of PDZD2 in BRCA samples. These findings suggest that alternative mechanisms may underlie PDZD2 dysregulation in BRCA. This observation highlights the complexity of PDZD2 regulation in cancer and prompts further investigation into additional molecular pathways and regulatory factors that may modulate PDZD2 expression and activity in BRCA. Understanding these alternative mechanisms could provide valuable insights into

the underlying biology of BRCA and uncover novel therapeutic targets for more effective treatment strategies.

Collectively, these findings highlight the multifaceted role of PDZD2 in cancer development and progression, emphasizing its potential as a biomarker for prognosis and a therapeutic target for intervention strategies.

5. Conclusion

In conclusion, our comprehensive analysis of PDZD2 expression, promoter methylation, survival outcomes, and mutational status in BRCA has provided valuable insights into the role of PDZD2 in BRCA development and progression. We observed significant down-regulation of PDZD2 expression in BRCA samples compared to normal controls, suggesting its potential involvement in BRCA proliferation. Additionally, promoter methylation analysis revealed significant hypomethylation of PDZD2 in BRCA, indicating potential epigenetic dysregulation. Survival analysis demonstrated a significant correlation between low PDZD2 expression and higher overall survival rates in BRCA patients, highlighting PDZD2 as a potential prognostic marker. However, mutational analysis showed minimal impact of genetic alterations on PDZD2 dysregulation in BRCA. These findings collectively underscore the complex regulatory mechanisms governing PDZD2 expression in BRCA and suggest the involvement of alternative pathways in its dysregulation. Further research is warranted to elucidate these mechanisms and explore the therapeutic potential of targeting PDZD2 in BRCA management.

6. Acknowledgment

None

7. References

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