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EXPLORING THE ROLE OF ANKRD1 IN BREAST INVASIVE CARCINOMA: EXPRESSION ANALYSIS, PROMOTER METHYLATION, AND PROGNOSTIC IMPLICATIONS THROUGH BIOINFORMATICS ANALYSIS

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Abstract

The present study deciphers the expression patterns and methylation status of ANKRD1, a potential biomarker, in breast invasive carcinoma (BRCA) using bioinformatics tools. Initially, ANKRD1 expression was analyzed in BRCA and normal control samples, revealing significant down-regulation in tumor samples compared to controls, indicating its potential role in BRCA progression. Subsequently, ANKRD1 expression was assessed across various clinical parameters, including cancer stages, patient demographics, and race. Notable discrepancies in ANKRD1 expression were

observed across different cancer stages, genders, ages, and racial backgrounds of BRCA patients, emphasizing its clinical significance in BRCA pathogenesis. Promoter methylation analysis revealed significant hypo-methylation of ANKRD1 in BRCA samples compared to normal controls, suggesting potential epigenetic regulation of ANKRD1 expression in BRCA. Furthermore, survival analysis using the KM plotter tool demonstrated a significant correlation between ANKRD1 expression levels and patient survival outcomes, with high ANKRD1 expression associated with poor overall survival in BRCA patients. Mutational analysis revealed minimal genetic alterations in ANKRD1 in BRCA samples, suggesting that genetic variations have limited impact on ANKRD1 dysregulation in BRCA. These findings underscore the potential of ANKRD1 as a prognostic marker and therapeutic target in BRCA management.

Key words: ANKRD1: Cancer: Biomarker: Prognosis

Introduction

Cancer represents a significant global burden, ranking as the second leading cause of death worldwide, with over one in six individuals succumbing to the disease (1-4). In 2020 alone, approximately 10 million people lost their lives to cancer on a global scale. Among the various types of cancer, breast invasive cancer (BRCA) stands out as one of the most prevalent and severe forms affecting women, ranking as the fifth leading cause of cancer-related deaths. An estimated 2.3 million new cases of breast cancer were reported in 2020 (5, 6).

Genetic mutations and DNA damage, often influenced by estrogen exposure, are primary factors contributing to the development of BRCA. Depending on the involvement of the basement membrane, BRCA can manifest as either invasive or non-invasive forms (6-8). Diagnostic techniques for cancer include mammography, ultrasonography, magnetic resonance imaging, and tissue biopsy, which aid in the detection and characterization of tumors (8, 9). Treatment modalities for BRCA typically encompass a range of approaches such as radiotherapy, hormonal therapy, chemotherapy, and targeted therapy (6, 10, 11). However, these conventional treatment methods may be associated with adverse side effects for patients.

Many patients exhibit limited response to emerging anti-cancer therapies like immune checkpoint blockade (ICB) therapy (12-14). Hence, there is a pressing need to identify common molecular mechanisms and novel diagnostic biomarkers (15, 16). Ankyrin repeat domain 1 (ANKRD1), also referred to as cardiac Ankyrin repeat protein (CARP), belongs to the conserved muscle Ankyrin repeat protein (MARP) family (17-20). There is a probable association between ANKRD1 expression and cancer-associated fibroblasts (CAFs) (21, 22). ANKRD1 is predominantly expressed in the heart and plays a specific role in myofibrillar assembly, signal transduction, and transcriptional regulation (17, 23). It is implicated in the Hippo/YAP signaling pathway, which is involved in various cellular processes including differentiation, proliferation, and cell death, as well as in numerous cancers (24, 25). Additionally, ANKRD1 regulates P53 and functions as a transcriptional co-activator (26).

Previous studies have demonstrated the expression of ANKRD1 mRNA in various tumors such as hepatoma and ovarian serous cystadenocarcinoma (OV) (27, 28). Additionally, overexpression of ANKRD1 has been linked to tyrosine kinase inhibitors (EGFR-TKIs) (29). Moreover, yes-associated protein (YAP) amplifies the metastatic potential of BRCA, and YAP expression is associated with ANKRD1 (30). Furthermore, the expression of ANKRD1 is implicated in Phenylbutyrate (PB) resistance, with PB exhibiting antitumor activity in BRCA (31). Hence, these findings underscore the role of ANKRD1 in BRCA. In our research, we employed various bioinformatics methods to investigate the role of ANKRD1 in BRCA.

Material and Methods

Expression analysis of ANKRD1 in BRCA

The UALCAN database is a widely utilized platform for cancer analysis (32, 33). Leveraging data from the TCGA platform, we employed UALCAN to investigate the expression of ANKRD1 between BRCA and normal cells. Notably, UALCAN offers accessibility to all users and provides valuable insights for cancer analysis (34). Additionally, we utilized the UALCAN database to explore ANKRD1 expression across various parameters, including patient's age, gender, and race.

Promoter methylation analysis of ANKRD1

We employed the UALCAN database to assess the promoter methylation level of ANKRD1 in BRCA. This database is extensively utilized to gather and evaluate data pertaining to RNA expression, DNA methylation, viral infections, and clinical features of cancer patients (35-37). Our analysis included examining the promoter methylation level of ANKRD1 across different parameters such as patient's age, gender, and race.

Survival analysis of ANKRD1

The Kaplan-Meier (KM) plotter is a widely utilized tool for survival analysis (38). In our study, we utilized the KM plotter to investigate the impact of ANKRD1 deregulation on the overall survival (OS) of BRCA patients. This platform provides accessibility and is commonly employed to assess the prognostic value of gene expression, particularly in measuring the influence of specific genes on the OS of BRCA patients.

Mutational analysis of ANKRD1

cBioPortal is an essential and user-friendly database in cancer genomic research (39). It facilitates researchers in analyzing genetic alterations, clinical pathways, and references across various cancers. In our study, we utilized this platform to conduct mutational analysis of ANKRD1 in BRCA.

Results

Expression analysis of ANKRD1 in BRCA and normal control samples

Initially, we examined the expression of ANKRD1 in BRCA and normal control samples, revealing variations in ANKRD1 expression between tumor and control samples. Utilizing the UALCAN database for analysis, we observed a significant down-regulation in ANKRD1 expression in BRCA samples (Figure 1), indicating a potential role for ANKRD1 in BRCA progression.

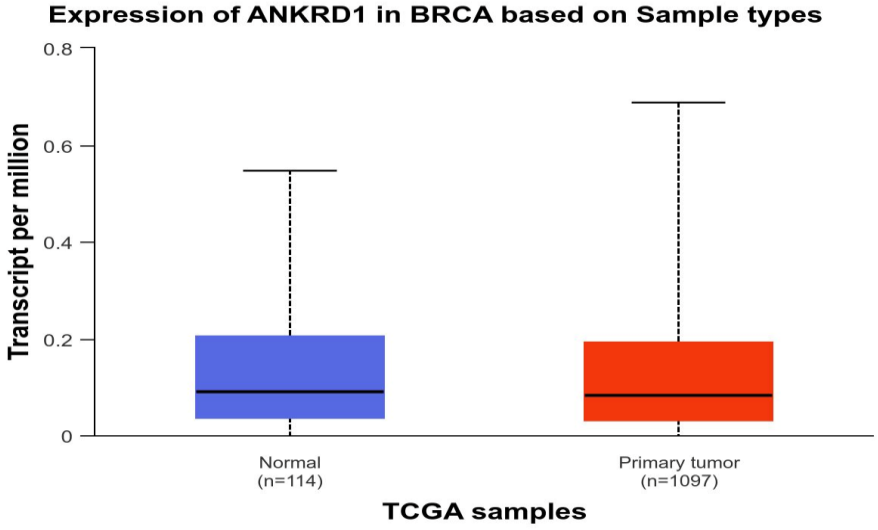

Figure 1: Expression profiling of ANKRD1 in BRCA and normal samples

Expression analysis of ANKRD1 in BRCA sample divided based on different parameters

Subsequently, we conducted an analysis of ANKRD1 expression in BRCA samples across various parameters, including Individual Cancer Stages, Patient's Age, Patient's Gender, and Patient's Race. Initially, we examined ANKRD1 expression in samples from patients at different cancer stages, revealing significant down-regulation in ANKRD1 across distinct BRCA stages (Figure 2A). Additionally, we assessed ANKRD1 expression in BRCA patients of different races, observing down-regulation in ANKRD1 expression compared to normal samples (Figure 2B). Further analysis based on patient gender revealed significant down-regulation of ANKRD1 expression in both female and male BRCA patients compared to normal samples (Figure 2C). Subsequent examination of ANKRD1 expression across different age groups demonstrated significant variations, with up-regulated expression in young patients and down-regulated expression in older patients (Figure 2D). Collectively, these analyses underscore the significant role of ANKRD1 in BRCA.

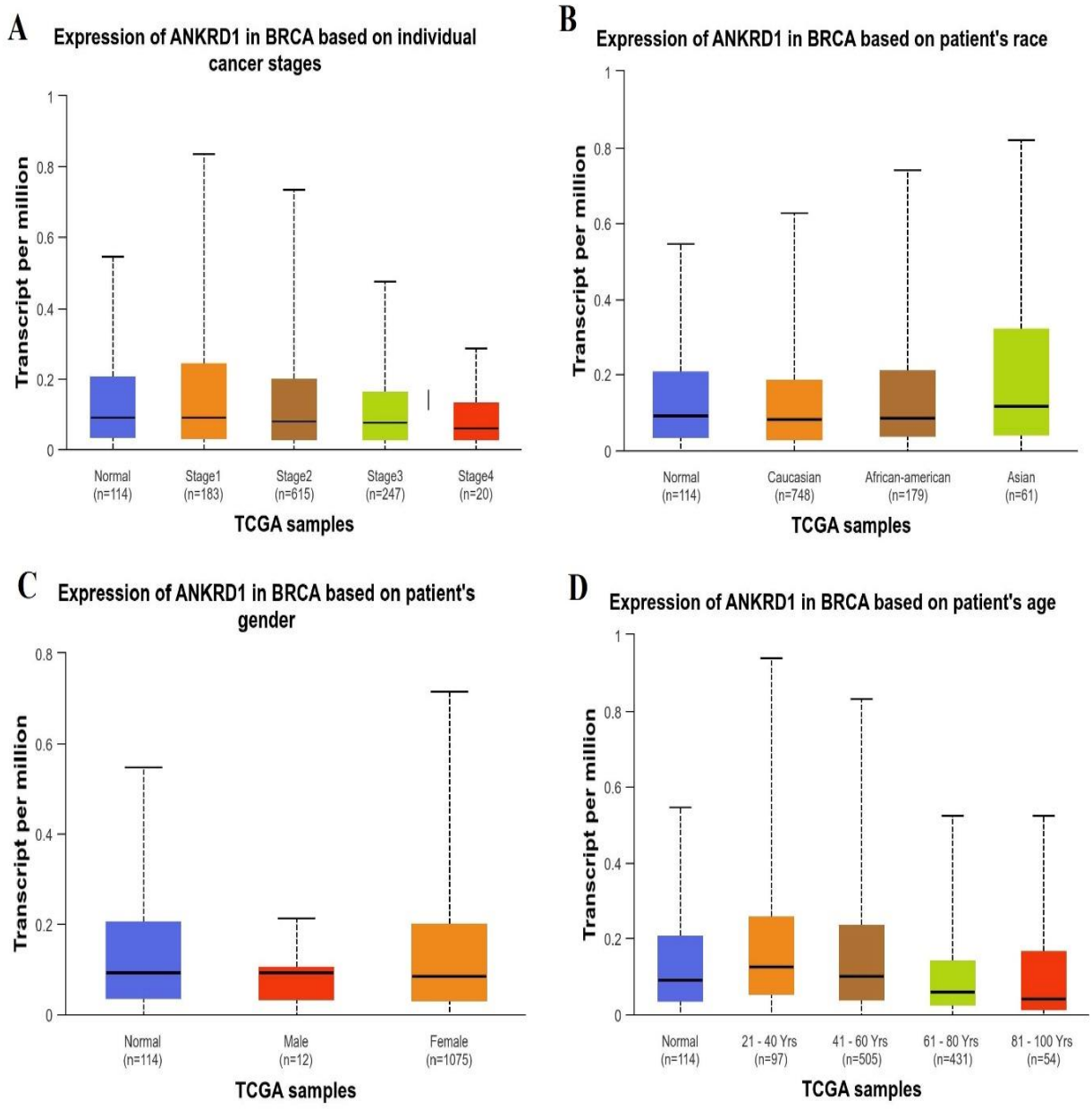

Figure 2: Expression profiling of ANKRD1 in normal and BRCA samples of different clinical variables

Promoter methylation of ANKRD1 in BRCA and normal control Samples

We employed the UALCAN database to investigate the promoter methylation status of ANKRD1 in BRCA samples compared to normal control samples (Figure 3). Previous research has emphasized the significance of promoter methylation in regulating gene expression (40). Our analysis revealed a significant hypo-methylation pattern in BRCA samples compared to normal samples.

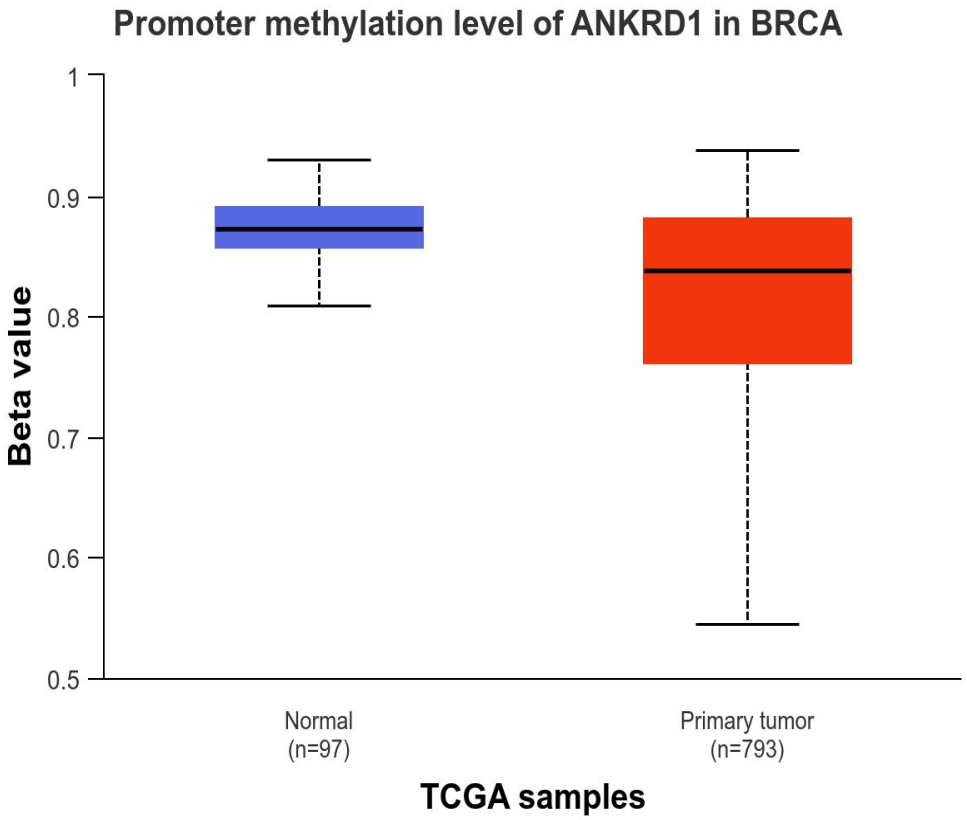

Figure 3: Promoter methylation profiling of ANKRD1 in BRCA and normal samples

Promoter methylation of ANKRD1 in BRCA sample divided based on different parameters

We examined the promoter methylation status of ANKRD1 in BRCA samples across various parameters including Individual Cancer Stages, Patient's age, Patient's Gender, and Patient's race. Initially, we assessed the promoter methylation of ANKRD1 at different BRCA stages and observed significant variations. Notably, we identified a consistent pattern of hypo-methylation in ANKRD1 levels across different BRCA stages (Figure 4A). Subsequently, we investigated ANKRD1 promoter methylation based on patient's race. Our analysis revealed divergent patterns in ANKRD1 expression between BRCA samples and normal samples (Figure 4B). Moving forward, we examined the ANKRD1 promoter methylation levels according to patient's gender, finding consistent hypo-methylation in ANKRD1 levels across both genders in BRCA samples (Figure 4C). Lastly, we explored ANKRD1 promoter methylation levels across different age groups of BRCA patients, observing variations in promoter methylation levels (Figure 4D). These findings underscore the potential impact of promoter methylation on ANKRD1 expression in BRCA across diverse patient demographics.

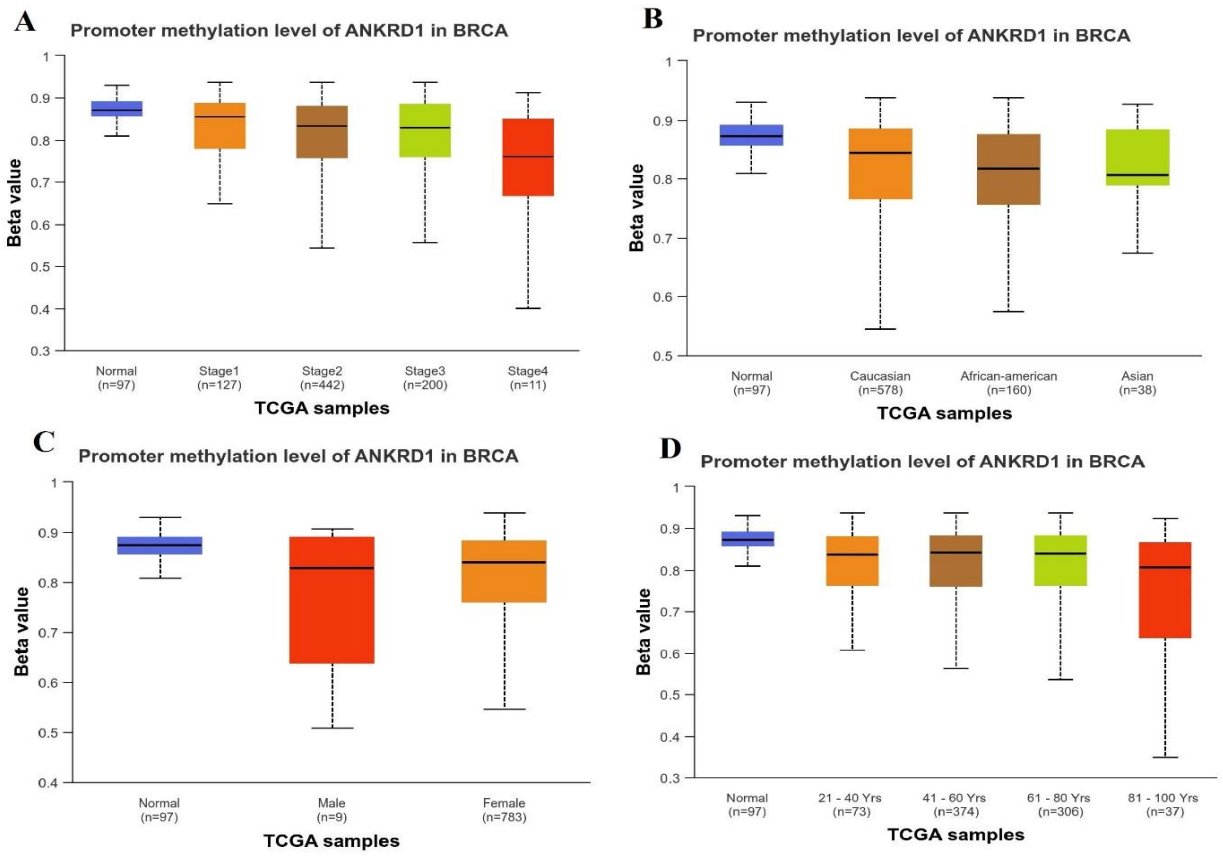

Figure 4: Promoter methylation profiling of ANKRD1 in normal and BRCA samples of different clinical variables

Survival analysis of ANKRD1

We employed the KM plotter tool to assess the clinical significance of the ANKRD1 gene in BRCA by evaluating patients' overall survival (OS). Our analysis indicated that BRCA patients with high ANKRD1 expression experienced lower OS rates, whereas those with low expression levels of ANKRD1 exhibited higher OS rates (Figure 5). These findings suggest that lower expression of ANKRD1 may adversely affect the survival outcomes of BRCA patients, highlighting the potential prognostic value of ANKRD1 expression in BRCA.

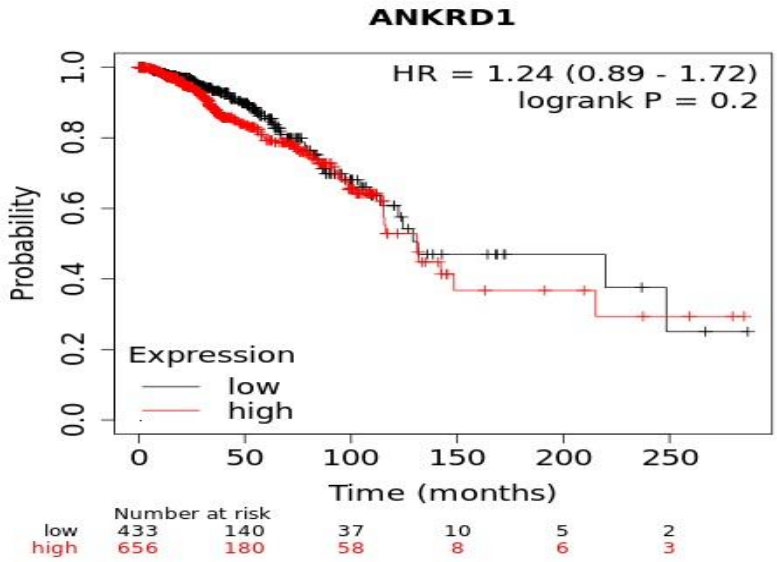

Figure 5

Mutational analysis of ANKRD1 in BRCA

We conducted a mutational analysis of PDZD2 in BRCA using the cBioPortal platform. Our analysis revealed a mutation rate of 0.7% in BRCA samples. The genetic alterations detected in ANKRD1 included amplification, deep deletion, and some missense mutations (Figure 6). However, we observed that these genetic variations had a low impact on the dysregulation of ANKRD1 in BRCA.

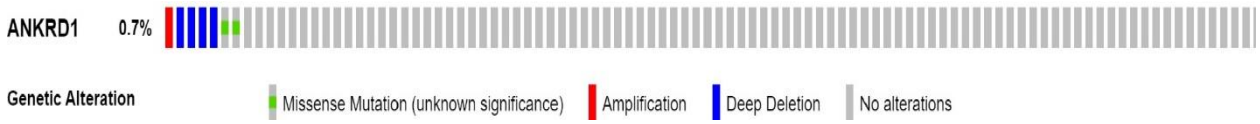

Figure 6: Mutatome map of ANKRD1 mutations in BRCA

Discussion

Our study aimed to investigate the clinical relevance of the ANKRD1 gene in breast cancer (BRCA), focusing on its expression, promoter methylation, and prognostic implications. We conducted a thorough analysis, comparing our findings with existing research.

Initially, we utilized the UALCAN database to examine the expression of ANKRD1 in BRCA and normal control samples. Our analysis revealed a notable down-regulation of ANKRD1 expression in BRCA samples compared to normal samples, with statistical significance p-value < 0.05. These findings underscore the significant role of ANKRD1 in suppressing BRCA, aligning with previous studies suggesting its function as a tumor suppressor gene and its influence on the expression of TP53 (41).

Based on these initial findings, we broadened our investigation to explore ANKRD1 expression in BRCA across various parameters, including Individual Cancer Stages, Patient's age, Patient's Gender, and Patient's race. Our analysis revealed significant variations in expression across these parameters, predominantly showing down-regulation in expression across different ages, levels of advancement, genders, and racial groups. This consistent pattern of abnormal expression underscores the potential of ANKRD1 as a diagnostic biomarker, highlighting its role in suppressing BRCA progression.

Promoter methylation is a crucial epigenetic process known to influence gene expression dynamics significantly (42, 43). Consequently, we examined the promoter methylation status of ANKRD1 expression in BRCA compared to normal samples, revealing a state of hypo-methylation in its expression. This hypo-methylation and the concurrent down-regulation in expression suggest an abnormal behavior of ANKRD1 in BRCA (44, 45). Building upon these findings, we further delved into the promoter methylation levels of ANKRD1 expression in BRCA across various parameters, including Individual Cancer Stages, Patient's age, Patient's Gender, and Patient's race. Our analysis consistently unveiled hypo-methylation in ANKRD1 expression across these parameters, underscoring the regulatory role of epigenetic modifications in shaping the expression landscape of ANKRD1 in BRCA.

Moreover, we conducted an analysis to explore the relationship between ANKRD1 expression and overall survival (OS) in BRCA through survival analysis. Our findings revealed a positive correlation, indicating that higher ANKRD1 expression corresponds to improved overall survival. This underscores the potential of ANKRD1 as a prognostic indicator in BRCA. Additionally, we performed mutational analysis using the cBioPortal platform. Although our analysis identified genetic variations, their impact on the dysregulation of ANKRD1 in BRCA appeared to be minor. However, further investigation is necessary to fully elucidate their significance. While our results align with previous studies on dysregulation in cancer, it is important to acknowledge certain limitations in our findings. Our examination primarily focused on under expression and hypo-methylation of ANKRD1, which may conflict with the findings of previous studies. Therefore, additional research is warranted to validate the anticipated effect of ANKRD1 in BRCA..

Conclusion

Our assessment provides a comprehensive analysis of ANKRD1 in BRCA, shedding light on its promoter methylation status, prognostic implications, and expression patterns. These findings suggest a potential role for ANKRD1 as a diagnostic and therapeutic biomarker in BRCA. However, further research is needed to reinforce these findings and establish a groundwork for future clinical applications of ANKRD1 in BRCA.

Conflict of interest

None

Acknowledgement

None

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