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Original Article

Auxiliary Diagnosis and Prognostic Value of Dehydrogenase/Reductase 2 (DHRS2) in Various Tumors

Zhongwu An [1], Weibo Bo [1], Jibao Qin [1], Ling Jiang [1], *Jie Jiang [2]

1. *Clinical Laboratory, The Affiliated Lianyungang Oriental Hospital, Xuzhou Medical University, Jiang Su, China*
2. *Department of Pharmacy, The Affiliated Lianyungang Oriental Hospital, Xuzhou Medical University, Jiang Su, China*

***Corresponding Author:** Email: lygdfyy@163.com

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Abstract

Background: As the most convenient and commonly used for clinical diagnosis, cancer biomarker has been widely used in the auxiliary diagnosis of tumors, the observation of curative effect, the judgment of prognosis, and the monitoring of the disease.

Methods: Pan-cancer analysis was used to validate the value of Dehydrogenase/Reductase 2 (DHRS2) as a tumor prognostic marker in various tumors. The relationship of DHRS2 to TMB and MSI was used to explain the effect of DHRS2 on genomic instability. Online cbioportal was used to analyze DHRS2 mutations in tumors. Finally, 33 clinical tumor samples were collected in 2021 who were enrolled into the Affiliated Lianyungang Oriental Hospital of Xuzhou Medical University, to verify the expression and diagnostic prognostic value of DHRS2.

Results: The expression of DHRS2 was up-regulated in a variety of tumors and had adverse effects on the overall survival, disease-free interval, and progression-free interval of tumor patients. DHRS2 was associated with tumor genome instability, confirming that DHRS2 was correlated with tumorigenesis. In addition, DHRS2 had different mutation sites in various tumors. DHRS2 was up-regulated and was a poor prognosis biomarker in clinical tumor samples.

Conclusion: DHRS2 was aberrantly expressed in tumors and has diagnostic prognostic value.

Keywords: Dehydrogenase/Reductase 2; Pan-cancer; Diagnostic; Prognostic marker

Introduction

In recent years, cancer has become one of the most serious diseases that endanger human health. Cancer ranks second in the world's total mortality due to disease, second only to cardiovascular disease (1). Malignant tumors tend to invade surrounding tissues and spread (metastasize) throughout the body through the circulatory or lymphatic system. Patients with advanced cancer develop wasting syndrome (cachexia), which can also cause neuropathic pain, nausea, and difficulty breathing (2). In terms of treatment, there have been surgical resection, chemotherapy and radiotherapy, among which chemotherapy is an important means of tumor treatment, but traditional chemotherapy has poor targeting, and drugs kill tumor cells and cause damage to nor-

mal tissues at the same time (3). Therefore, improving the level of diagnosis and treatment of malignant tumors is urgently needed.

Tumor biomarkers refer to special substances that are produced or changed when malignant lesions occur in the body, resulting in some abnormal functions. It plays an important role in the screening, auxiliary diagnosis, treatment and prognosis of malignant tumors (4). Carcinoembryonic antigen (CEA) is a broad-spectrum tumor marker, and it is a good marker for evaluating the efficacy, condition and prognosis of tumors. Common serum tumor markers include CA153 and CA125 (5, 6). Common tumor markers such as AFP, FER, PRL, CEA, CA125, CA153, etc. can make up for the lack of imaging examinations to a certain extent (7-10). After continuous research and exploration, more and more new tumor markers have been discovered, such as cytokines, carbohydrate antigens, tumor miRNAs, etc., which have greatly improved the detection rate of malignant tumors. Finding sensitive, specific and reliable biomarkers to provide evidence for early screening and diagnosis of patients is a top priority, but the search for non-invasive and easy-to-obtain specific biomarkers remains to be elucidated (11, 12).

Materials and Methods

Acquisition of Patient Data

RNA-seq expression and clinical information of pan-cancer patients were obtained from The Cancer Genome Atlas (TCGA) data portal (https://cancergenome.nih.gov/). TCGA is a joint project launched by the National Cancer Institute and the National Human Genome Research Institute in 2006, which currently studies a total of 33 types of cancer. The collected clinical samples included carcinoma and adjacent tissues from 6 adrenocortical carcinoma (ACC), 10 head and ceck squamous cell carcinoma (HNSC), 7 kidney renal clear cell carcinoma (KIRC), and 10 uterine corpus endometrial carcinoma (UCEC) patients from The Affiliated Lianyungang Oriental Hospital of Xuzhou Medical University for detection of gene expression in the year 2021.

This study has been approved by the Ethics Committee of the Affiliated Lianyungang Oriental Hospital of Xuzhou Medical University (approval no. 2021164), and all the patients signed the informed consent.

Kaplan-Meier survival analysis was performed for overall survival, disease-specific survival, disease-free interval, and progression-free interval.

The MSI score and TMB score was obtained from TCGA. The Spearman's method was used to analyze the correlation between cancer gene expression and MSI or TMB, using the "cor.test" command. A radar map was used to visualize indicators, which was designed using the R-package "fmsb".

Correlation of gene expression with tumor immune microenvironment in pan-cancers

Immune and stromal cell scores were calculated after applying the ESTIMATE algorithm in R-package "estimate" and "limma", for predicting tumor purity as well as the presence of infiltrating stromal/immune cells in pan-cancer tissues. A correlation analysis of gene expression with the tumor immune microenvironment was pursued using the R-package "ggplot2", "ggpubr" and "ggExtra" ($P < 0.001$ as a cut-off value) (13).

cBioPortal online analysis

We performed gene mining and analysis on the cBioPortal (https://www.cbioportal.org/), and selected the TCGA ACC, HNSC, KIRC, UCEC database for "Explore Selected Studies". Then we clicked the "Plots" and "Mutations" modules to perform gene mining analysis.

Immunohistochemistry (IHC).

Human ACC, HNSC, KIRC, UCEC samples and adjacent normal tissues were used for IHC staining. IHC was performed according to the manufacturer's instructions (cat. no. SP9001; ZSGB-BIO). The primary antibody (anti-DHRS2, 15735-1-AP, proteintech) were used for IHC. The specific operation steps were performed as previously described (14). The protein expression

level was determined according to the staining intensity and the percentage of immunoreactive cells.

Quantitative Real Time PCR.

RNA extraction, reverse transcription, and PCR amplification were performed according to the manufacturer's instructions (Takara Bio, Inc.). The specific operation steps were performed as previously described (15). The primer sequences were as follows: GAPDH sense, 5'-TGAGGTCCACCACCCTGTTG-3' and antisense, 5'- GTCAAGGCTGAGAACGGGAAG-3'; DHRS2 sense, 5'- TACCACCCTGAGGTCCCTTG -3' and antisense, 5'- GGCTGGTTTCATCCCTGTGC-3'. All reactions were performed in triplicate. GAPDH was used as an internal reference, and the relative expression of target gene was calculated using the 2-ΔΔCq method.

Statistical analysis

The R software (version 3.6.3) and GraphPad Prism software (version 7.0) was used to perform statistical analysis. Student's t-tests were used to conduct differential comparisons of two groups. one-way ANOVA was used to compare multiple independent samples. The predictive value of DHRS2 diagnosis prognostic in tumors was evaluated by the receiver operating characteristic (ROC) curve. *P* value <0.05 considered to be statistically significant.

Results

DHRS2 is prognostic, high expression is unfavorable in ACC, HNSC, KIRC, UCEC

Pan-cancer analysis was used to explore the impact of DHRS2 on various cancers. We found that DHRS was upregulated in HNSC, KIRC, UCEC and other tumors (Fig. 1A). Next, we analyzed the effect of DHRS2 on the survival of the above tumors. Among the above tumors, patients with high DHRS2 expression had shorter overall survival than those with low expression (Fig. 1B-E).

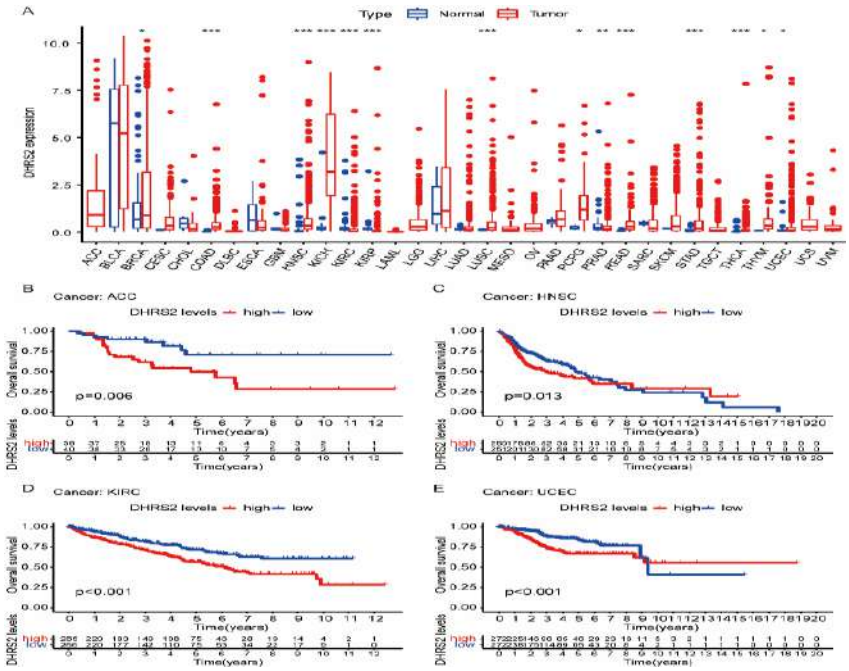

Fig. 1: DHRS2 is prognostic, high expression is unfavorable in ACC, HNSC, KIRC, UCEC.(A) The expression of DHRS2 in 33 cancers. *<0.05, ** *P*<0.01, *** *P* <0.001. (B-E) The overall survival of DHRS2 in ACC, HNSC, KIRC, UCEC. ACC: Adrenocortical carcinoma, HNSC: Head and Neck squamous cell carcinoma, KIRC: Kidney renal clear cell carcinoma, UCEC: Uterine Corpus Endometrial Carcinoma

In addition, although the expression of DHRS2 was not significantly different in different stages of tumors (Fig. 2C, F). DHRS2 had significant effects on disease-specific survival (Fig. 2A, D, G, $P < 0.01$), disease-free interval (Fig. 2H, $P = 0.021$), and progression-free interval (Fig. 2B, E, I, $P < 0.01$) of ACC, KIRC, and UCEC had different degrees of adverse prognostic effects.

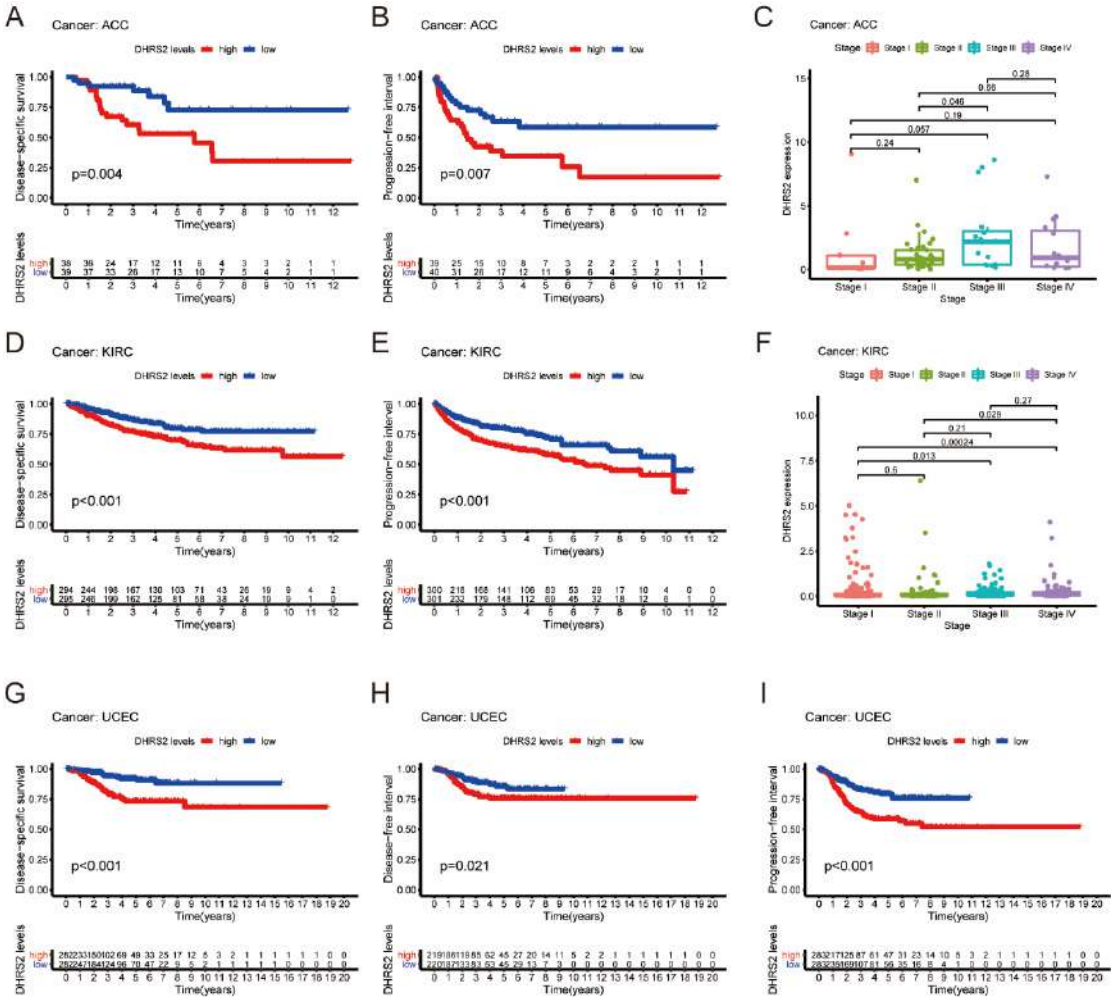

Fig. 2: DHRS2 has prognostic value in tumors. (A, D, G) The disease-specific survival of DHRS2 in ACC, KIRC, and UCEC. (Fig. 2B, E, I) The progression-free interval of DHRS2 in ACC, KIRC, and UCEC. (Fig. 2H) The disease-free interval of DHRS2 in UCEC. (C, F) The expression of DHRS2 in AJCC Stage of tumors. ACC: Adrenocortical carcinoma, HNSC: Head and Neck squamous cell carcinoma, KIRC: Kidney renal clear cell carcinoma, UCEC: Uterine Corpus Endometrial Carcinoma

The relationship between DHRS2 and tumor mutation burden and tumor immunity

Next, we analyzed the potential role of DHRS2 in tumors. DHRS2 positively correlated with TMB in tumors such as ACC, UCEC (Fig. 3A). In the correlation analysis with MSI, only a few tumors (UCEC) were significantly associated with DHRS2 (Fig. 3B). In addition, we performed immune correlation analysis. DHRS2 was negatively correlated with immune score and stromal score (Fig. 3C, D) and positively correlated with eosinophils (Fig. 3E) in ACC. DHRS2 positively correlated with dendritic cell activated in HNSCs (Fig. 3F). DHRS2 was negatively correlated with

dendritic cell resting, T cells regulatory in UCECs (Fig. 3G, K), and positively correlated with macrophage M1, T cell CD4 memory activated, and T cell follicular helper (Fig. 3H-J). We also analyzed the correlation of DHRS2 with immune-related genes. ACC, HNSC, UCEC were correlated with a few immune-related genes, while KIRC was associated with most immune-related genes (Fig. 4A).

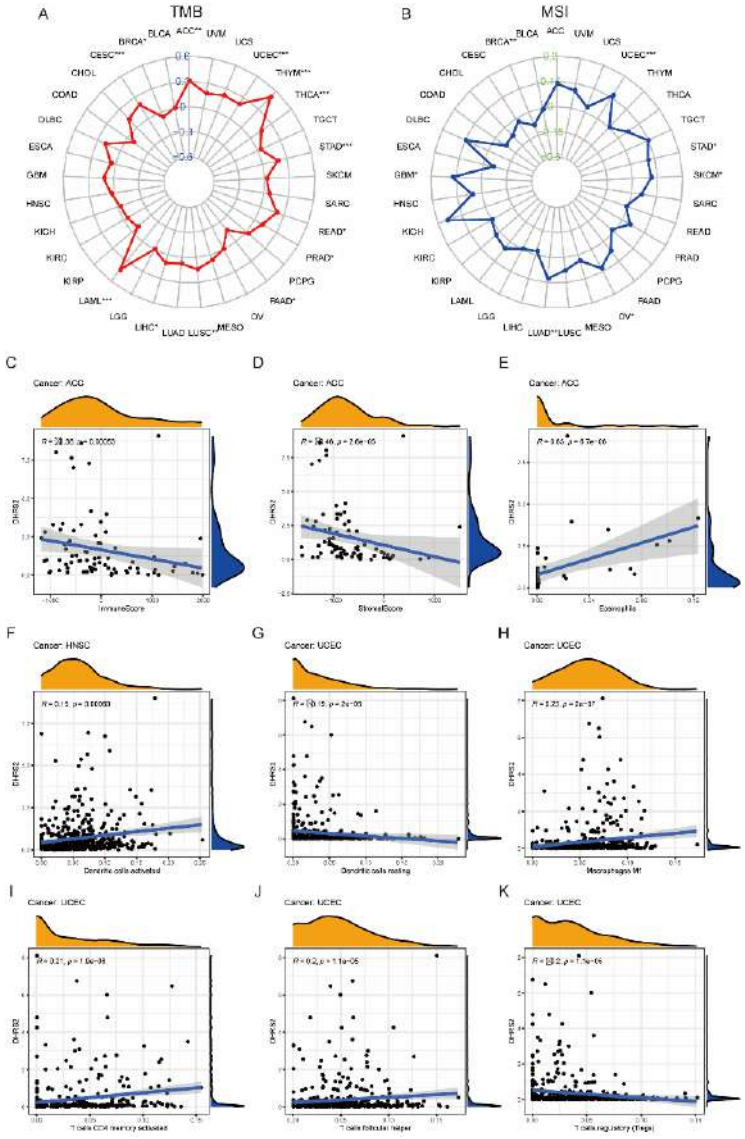

Fig. 3: Pan-cancer analysis of DHRS2.
(A) The relationship between DHRS2 and TMB in 33 cancers. (B) The relationship between DHRS2 and MSI in 33 cancers. (C-K) The relationship between DHRS2 and tumor immune microenvironment in ACC, HNSC, KIRC, UCEC. TMB, tumor mutational burden. MSI, Microsatellite instability. ACC: Adrenocortical carcinoma, HNSC: Head and Neck squamous cell carcinoma, KIRC: Kidney renal clear cell carcinoma, UCEC: Uterine Corpus Endometrial Carcinoma

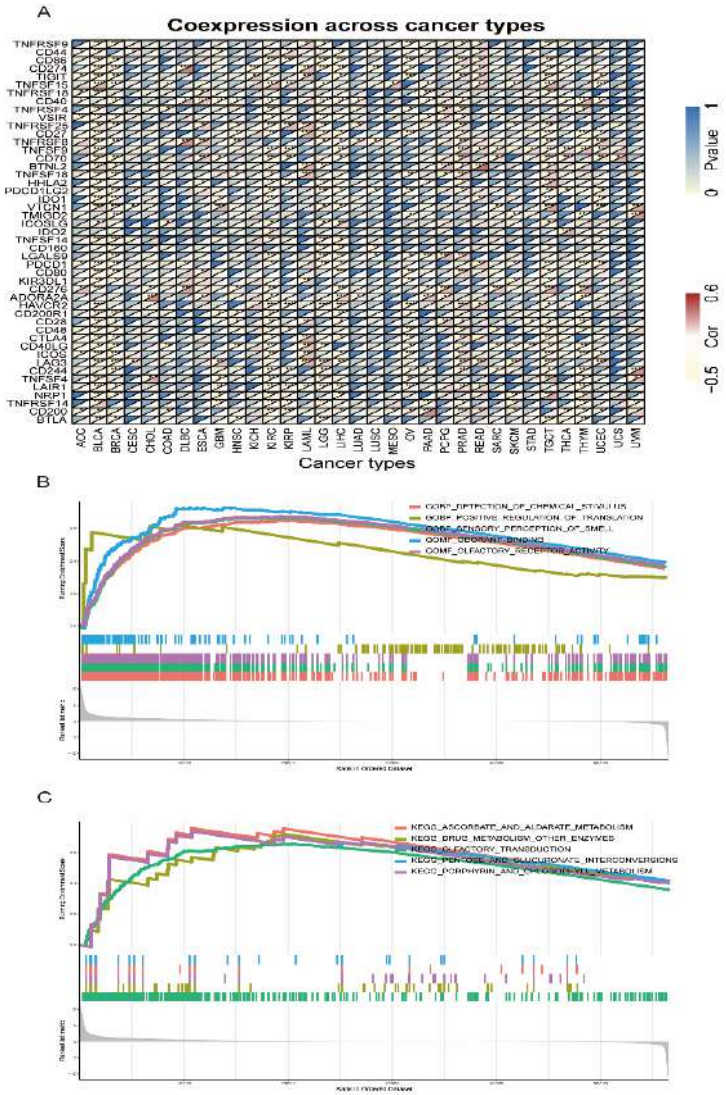

Fig. 4: Analysis of DHRS2 and Immune related genes.
(A) The correlation coefficients between expression of DHRS2 and immune related genes in tumors. (B, C) The GO and KEGG analysis results shown that DHRS2 was related to detection of chemical stimulus, positive regulation of translation, ascorbate and aldarate metabolism, and drug metabolism other enzymes, etc

The biological function of DHRS2 in tumors

We performed GO and KEGG analysis of DHRS2 in multiple tumors. In UCEC, DHRS2 was associated with detection of chemical stimulus, positive regulation of translation, ascorbate and aldarate metabolism, and drug metabolism other enzymes (Fig. 4B, C). Next, we performed an online analysis of possible mutations in DHRS2 in different tumors. DHRS2 had no mutation site in ACC (Fig. 5A), but had mutational state of shallow mutation, diploid, and gain (Fig. 5E). DHRS2 had a missense mutation of E83G in HNSC (Fig. 5B) and mutational state of deep deletion, shallow deletion, diploid, gain, and amplification (Fig. 5F). In KIRC, a missense mutation of DHRS2 is H93R (Fig. 5C) and mutational state of shallow deletion, diploid, and gain (Fig. 5G). Finally, missense mutation of I65V and a X47 splice mutation of DHRS2 were found in UCEC (Fig. 5D) and mutational state of shallow deletion, diploid, and gain (Fig. 5H).

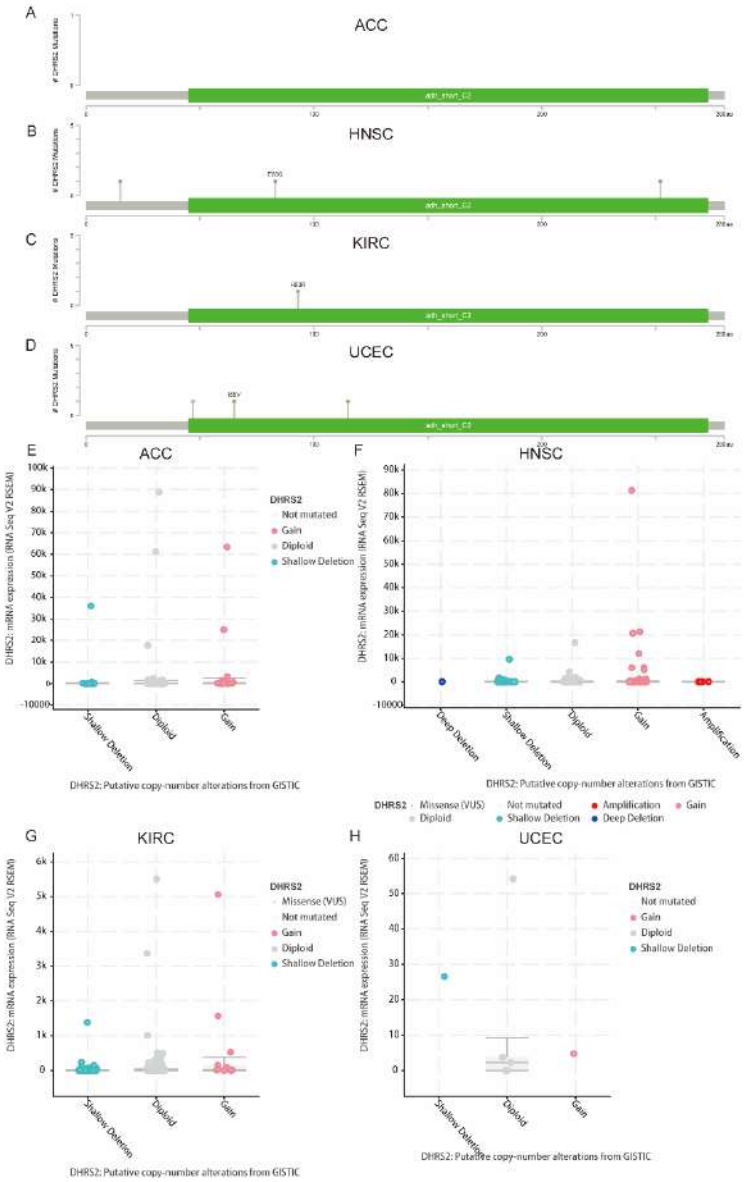

Fig. 5: Analysis of gene characteristics of DHRS2 in tumors.
(A-D) The mutation site of DHRS2 in ACC, HNSC, KIRC, UCEC. (D) The relationship between DHRS2 mRNA expression and deep deletion, shallow deletion, diploid, gain, and amplification variation. ACC: Adrenocortical carcinoma, HNSC: Head and Neck squamous cell carcinoma, KIRC: Kidney renal clear cell carcinoma, UCEC: Uterine Corpus Endometrial Carcinoma

DHRS2 has tumor diagnostic and prognostic value

Finally, we validated DHRS2 expression in collected tumor specimens. The results showed that DHRS mRNA2 was up-regulated in ACC, HNSC, KIRC and UCEC (Fig. 6A-D). Meanwhile, immunohistochemistry also showed that the protein expression level of DHRS was up-regulated in tumors (Fig. 6E-H). In addition, the ROC curves also indicated that DHRS2 had a high diagnostic and prognostic value for tumors (ACC: AUC=0.722, HNSC: AUC=0.721, KIRC: AUC=0.708, UCEC: AUC=0.716, Fig. 7A-D).

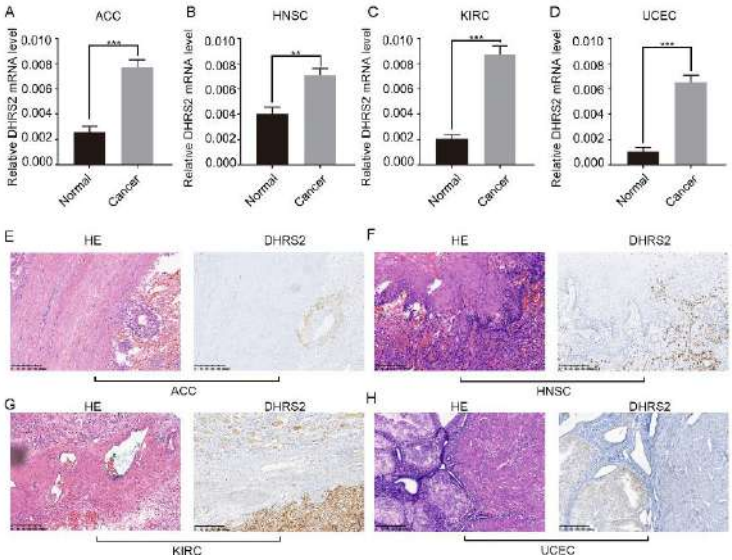

Fig. 6: DHRS2 was up-regulated in cancer samples.
(A-D) DHRS2 mRNA expression in normal tissues and tumor adjacent to ACC, HNSC, KIRC, UCEC. (E-H) Immunohistochemical staining (DHRS2) of normal tissues adjacent to cancer and ACC, HNSC, KIRC, UCEC (×200). Data are presented as mean ± standard deviation, ** P<0.01, *** P<0.001. ACC: Adrenocortical carcinoma, HNSC: Head and Neck squamous cell carcinoma, KIRC: Kidney renal clear cell carcinoma, UCEC: Uterine Corpus Endometrial Carcinoma

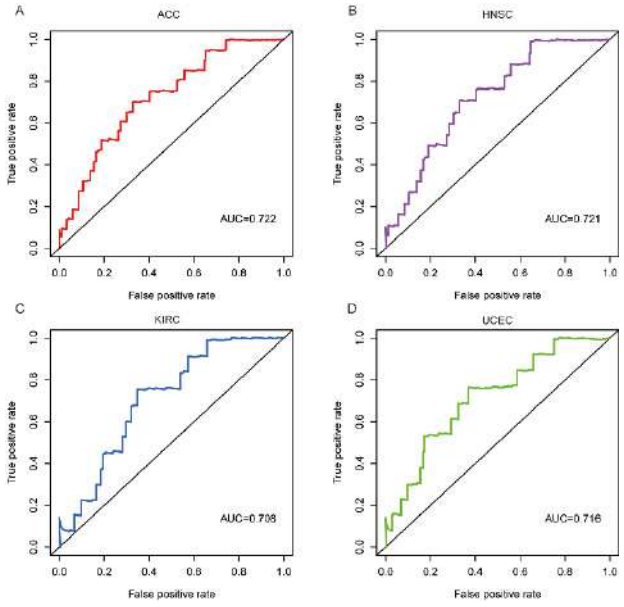

Fig. 7: DHRS2 has tumor diagnostic and prognostic value.
(A-D) The ROC curves of DHRS2 in ACC, HNSC, KIRC, UCEC samples. ACC: AUC=0.722, HNSC: AUC=0.721, KIRC: AUC=0.708, UCEC: AUC=0.716. ROC: receiver operating characteristic curve. ACC: Adrenocortical carcinoma, HNSC: Head and Neck squamous cell carcinoma, KIRC: Kidney renal clear cell carcinoma, UCEC: Uterine Corpus Endometrial Carcinoma

Discussion

In this study, we found that Dehydrogenase/Reductase 2 (DHRS2) was aberrantly expressed in a variety of tumors and had diagnostic prognostic value. We performed a pan-cancer analysis and found that DHRS2 was up-regulated in a variety of tumors and had adverse effects on the overall survival, disease-free interval, and progression-free interval of patients. Next, we found that DHRS2 is associated with tumor mutational burden (TMB) and microsatellite instability (MSI), further confirming that DHRS2 is associated with tumorigenesis. Furthermore, we found that DHRS2 has different mutation sites in various tumors. Finally, the expression and diagnostic prognostic value of DHRS2 in tumors with clinical samples were validated.

Tumors are one of the leading causes of human death. Due to the clinical symptoms of malignant tumors are not obvious in the early stage, it is difficult to achieve early detection. Patients with clinically diagnosed malignant tumors are often in the middle and late stages, the clinical treatment effect is poor, and the mortality and recurrence rates are high (16). According to the WHO estimates, there are about 10 million new cases of malignant tumors in the world each year, and nearly 7 million people die from tumors, and the number is increasing year by year (17). Therefore, the early detection, early diagnosis and early treatment of malignant tumors are the keys to improve the survival rate and cure rate of patients, and are of great significance in the prevention and treatment of malignant tumors. The research and diagnosis of the sensitivity and specificity of tumor biomarkers has become a hot topic in the study of tumor diagnosis (18). In this study, DHRS2 was aberrantly expressed in a variety of tumors and has diagnostic prognostic value.

The DHRS2 belongs to superfamily of short-chain dehydrogenases /reductases (SDR) and encodes an NAD/NADP-dependent oxidoreductase (19). DHRS2 is located on human chromosome 14q11.2, abnormally expressed in many tumors and plays an important role in tumorigenesis and malignant progression. Recent studies have shown that DHRS2 is involved in various tumor processes. For example, DHRS2 is highly expressed in esophageal squamous cell carcinoma, and silencing of DHRS2 promotes the apoptosis of esophageal squamous cell carcinoma cells and inhibits their migration and invasion ability (20). Furthermore, DHRS2 expression was associated with drug resistance in acute myeloid leukemia and gastric cancer (21, 22). DHRS2 in nasopharyngeal carcinoma inhibits the growth of tumor cells in vivo and in vitro. It can be used as a target for the antitumor drug varicin in the treatment of nasopharyngeal carcinoma (23). Consistent with the above studies, DHRS2 was highly expressed in a variety of tumors, such as ACC, HNSC, KIRC, and UCEC, and the analysis of overall survival, disease-free interval, and progression-free interval all suggested that DHRS2 has a poor prognostic effect on tumors. In addition, we also found that the expression of DHRS2 in tumor samples was consistent with the results of our analysis, and the ROC curve proved its good diagnostic and prognostic value. Of course, there are also reports that differ from the results of this study, such as decreased DHRS2 expression in ovarian cancer tissues, and high DHRS2 expression in ovarian cancer patients is associated with better prognosis (24). Therefore, the roles of DHRS2 in different types of tumors may be inconsistent.

DHRS2 was also positively associated with TMB and MSI in tumors, suggesting that it may affect genomic instability. Previous studies have shown that DHRS2 reduces MDM2-mediated degradation of P53 by binding to MDM2, thereby stabilizing and activating P53 (22, 25). As a transcription factor, p53 can affect a series of downstream gene expression changes when activated. p53 expression was up-regulated after cells were exposed to DNA-damaging drugs, suggesting that it may be involved in promoting DNA repair (26). P53 could inhibit the DNA damage caused by cisplatin by binding to the ERCC1 promoter and enhancing its expression (27).

DHRS2 is specifically expressed in DCs differentiated from immature monocytes but not detected in other hematopoietic cells such as neutrophils, monocytes or macrophages. When treated with inflammation-inducing factors such as lipopolysaccharide (LPS) and tumor necrosis factor (TNF), DHRS2 mRNA levels in DCs were subsequently downregulated (28). Consistent with previous studies, we found that DHRS2 was associated with immune cells, especially DCs, in a variety of tumors. Because DCs play a key role in inducing immune responses and tolerance, they may be developed as important targets for the immune system and gene therapy for disorders of the abnormal immune system, including rheumatoid arthritis, allergic reactions, and cancer (29). Therefore, uncovering the mechanism of DHRS2 expression in DCs may pave the way for immunotherapy using DCs as a tool.

The strength of this study lies in the use of pan-cancer analysis to highlight the adverse prognostic effect of DHRS2 on tumors, and the use of TMB, MSI and mutational analysis to verify the value of DHRS2 in tumors. In addition, this study has many limitations. 1) Other suitable datasets have not been found to test the role of DHRS2 in tumors. 2) Only cancer and paracancerous samples were taken for verification. In order to determine further the diagnostic value of DHRS2 for tumors, we will design experiments to verify the diagnostic value of DHRS2 in serum of tumor patients in future experiments.

Conclusion

DHRS2 has tumor diagnostic and prognostic value in ACC, HNSC, KIRC, UCEC.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interests

The authors declare that there is no conflict of interest.

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