

Aberrant brain-expressed X-linked 4 (BEX4) expression is a novel prognostic biomarker in gastric cancer

Chenhong Zhu, MD, Deshuang Xiao, MD* 

Abstract

Background: This study aimed to investigate the expression level of X-linked 4 (BEX4) in patients with gastric cancer (GC) and to investigate the prognostic significance of BEX4.

Methods: The mRNA expression of BEX4 was analyzed using the Cancer Genome Atlas (TCGA) datasets. The relationship between the expression of BEX4 and GC patient survival was assessed using a Kaplan-Meier plot and Log Rank test. Multivariate cox regression analysis was used to evaluate prognostic factor. The diagnostic value of BEX4 expression in GC tissue was determined through receiver operating characteristic (ROC) curve analysis. Gene set enrichment analysis (GSEA) was used to explore BEX-4 related signaling pathways in GC. Furthermore, the Human Protein Atlas (HPA) database and GSE62254 dataset were used for further validation.

Results: BEX4 was expressed at lower level in GC tissues than normal gastric tissues. The lower expression of BEX4 was also validated at protein level in HPA database. The area under the ROC curve for BEX4 expression in normal gastric tissue and GC was 0.791, which presented modest diagnostic value. Kaplan-Meier survival analysis revealed that patients in low BEX4 expression group had a worse prognosis than those with high BEX4 expression ($P = .009$). Multivariate analysis showed that BEX4 is an independent risk factor for overall survival both in TCGA and GSE62254 ($P = .0142, .013$, respectively). GSEA identified that the expression of BEX4 was related to DNA replication, RNA polymerase, cell cycle, and P53 signaling pathway.

Conclusion: BEX4 is expressed at low levels in GC. BEX4 expression independently predicted poor OS for GC. It is a promising independent molecular predictor for the diagnosis and prognosis of GC.

Abbreviations: AUC = area under curve, BEX4 = brain-expressed X-linked 4, GC = gastric cancer, GEO = Gene Expression Omnibus, GSEA = Gene set enrichment analysis, HPA = Human Protein Atlas, HR = Hazard ratio, OR = Odds ratio, OS = overall survival, ROC = receiver operating characteristic, TCGA = The Cancer Genome Atlas.

Keywords: brain-expressed X-linked 4, gastric cancer, diagnosis, prognosis, TCGA database

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All the data in this study are available from TCGA database

Our study did not require an ethical board approval because the raw data of this study are derived from the TCGA database and GEO database, both of which are publicly available databases. All detailed data included in the study are available to all.

The authors have no conflicts of interest to disclose.

(<https://portal.gdc.cancer.gov/repository>) and GEO database (<https://www.ncbi.nlm.nih.gov/geo/>).

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Department of General surgery, The First People's Hospital of WenLing, Wenling, Zhejiang, China.

* Correspondence: Deshuang Xiao, Department of General Surgery, The First People's Hospital of Wenling, No. 333, Chuan'an South Road, Chengxi Street, Wenling 317500, China (e-mail: xiaodeshuang456@163.com).

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1. Introduction

Gastric cancer (GC) is a serious health problem worldwide, as it remains the fourth most common malignancy and the second dominant cause of cancer-associated death.^[1] In recent years, approximately 60% of all new cases have been diagnosed in China, Japan, and Korea.^[2] It was estimated that approximately 24,590 new cases and 10,720 GC related deaths occurred in 2015 in the United States.^[3] Although there has been a gradual decrease in the incidence of GC over the past decades, the number of survivors is relative low, since diagnosis is often determined during the late stages when obvious symptoms appear or even metastasis, which brought heavy burden to global health.^[4,5] Hence, identifying novel biomarkers related to diagnose and prognosis of GC are urgently needed.

In recent years, many studies have been done to identify molecular prognostic biomarkers for GC.^[6–8] Brain-expressed X-linked 4 (BEX4), located on human chromosome Xq22, belongs to the BEX family members. Human BEX4 is highly expressed in heart, skeletal muscle, and liver.^[9] Evidences have exhibited that BEX4 may serve as a tumor suppressor in lung adenocarcinoma, ovarian cancer, and oral squamous cell carcinoma.^[10–12] BEX4 displayed distinct tissue distribution and had varying roles dependent on different cellular context. However, so far, little is known about the role of BEX4 in the diagnosis and prognosis of GC. Therefore, in the present study, we first explored the expression patterns and prognosis of BEX4 in GC.

2. Materials and methods

2.1. Data collection

The mRNA expression data of BEX4 in GC were downloaded from the TCGA (<https://portal.gdc.cancer.gov/>) database, which contained 375 human GC tissues and 32 normal gastric tissues. We then obtained clinical data of 443 patients, among those 435 with complete survival information. In addition, BEX4 expression data (GSE62254) for GC were downloaded from the Gene Expression Omnibus (<https://www.ncbi.nlm.nih.gov/geo/>) database, which contained 300 gastric tumors samples. We merged the mRNA expression data of BEX4 and clinical data and further analyzed the relationship between expression of BEX4 and clinical variables including age, gender, T stage, N stage, and M stage, pathological stage, histological grade, helicobacter pylori infection, cancer subtype, and regions. Then, the GC patients were divided into high expression and low expression groups based on median value of BEX4 expression and analyzed their differences in overall survival (OS).

2.2. Gene set enrichment analysis

GSEA assay was performed to investigate the potential mechanisms underlying the effect of BEX4 expression on GC prognosis. GSEA was performed in TCGA cohort using the software GSEA v2.2.2. The BEX4 expression level was annotated as high or low phenotype. GSEA was performed to explore the significant survival difference observed between high- and low-BEX4 groups. Gene set permutations were conducted 1000 times for each analysis. All other parameters were set to default.

2.3. Statistical analysis

The expression of BEX4 between GC cancer and normal gastric tissues in the TCGA cohort was evaluated using box plots. The relationship between expression levels of BEX4 and clinical variables was analyzed using the Wilcoxon signed-rank test, Kruskal-Wallis test and logistic regression. A ROC curve was generated to evaluate the diagnostic value of BEX4 expression, and the area under curve (AUC) of ROC curve represents the diagnostic value. An AUC value of more than 0.75 was deemed an excellent predictive value. Univariate Cox analysis was used to screen possible prognostic variables. The variables determined by univariate analysis with $P < .05$ were considered as candidates for the multivariate Cox analysis. Using the Cox proportional hazards model, the independent prognostic factors of survival were analyzed by multivariate analysis. P value $< .05$ was regarded as statistically significant. All statistical analyses were performed using R software (V.3.5.1).

2.4. Validation in HPA and GEO databases

The HPA is a pathology tool that provides numerous protein expression profiles of various human proteins. In the database, protein expression scoring is manually conducted by combined evaluation of the fraction of stained cells ($< 25\%$, $25\%–75\%$ or $> 75\%$) and staining intensity (negative, weak, moderate or strong). Therefore, we compared the expression of BEX4 in normal and GC tissues at protein level using immunohistochemistry data from the HPA database (<http://www.proteinatlas.org/>). To ensure the accuracy of the results from the TCGA cohort, GSE62254 was used to validate whether BEX4 was remain an independent predictor of GC prognosis in an external cohort.

3. Results

3.1. Association of BEX4 expression with clinical variables

The clinical data pertaining to 443 GC patients from the TCGA were analyzed, including the patient's age, gender, histologic grade, pathological stage, helicobacter pylori infection, T stage, N stage, and M stage, different types of gastric cancer, survival status, survival time, and the specific regions. As shown in Figure 1 (A–K), differences in BEX4 expression were significantly correlated with age, histologic grade, pathological stage, T stage, patients survival status, subtypes of gastric cancer, and the cancer regions (all $P < .05$). Expression levels of BEX4 in 375 GC and 32 normal gastric tissues were compared using Wilcoxon signed-rank test, and the results revealed that BEX4 was lower expressed in GC compared to normal tissues ($P < .001$) (Figure. 2A). We identified 27 pairs of GC tissues and matched adjacent tissues from the TCGA cohort, and the expression levels of BEX4 in the paired tissues remained significantly under-expressed in GC tissues ($P < .001$, Fig. 2B). These results revealed that BEX4 is a tumor-suppressor in GC. Logistic regression analysis demonstrated that decreased BEX4 expression in GC was obviously correlated with age (OR = 0.583 for ≥ 65 vs < 65 , $P = .0115$), TNM stage (OR = 2.475 for stage II vs. stage I, $P = .0118$; OR = 2.266 for stage III vs. stage I, $P = .0181$), histological grade (OR = 5.376 for G3 vs G1, $P = .036$), T classification (OR = 3.534 for T3 vs T1, $P = .033$; OR = 3.655 for T4 vs T1, $P = .0321$), cancer subtype (OR = 0.569 for diffuse vs adenocarcinoma, $P = .006$; OR = 0.251 for tubular vs adenocarcinoma, $P = .00018$) (Table 1).

3.2. Diagnostic and prognostic value of BEX4 expression in GC

To evaluate the diagnostic value of BEX4, we generated a ROC curve using the expression data from the 375 GC patients and 32 healthy individuals. The area under the ROC curve (AUC) was 0.791 (95%CI: 74.8%–82.9%), which presented excellent diagnostic value (Fig. 2C). Moreover, the diagnostic performance of BEX4 among different subtypes of GC was performed. The AUC was 0.705 (95%CI: 59.4%–81.5%) for diffuse type stomach adenocarcinoma, 0.794 (95%CI: 70.8%–88.0%) for stomach adenocarcinoma, and 0.876 (95%CI: 80.5%–94.6%) for tubular stomach adenocarcinoma (Fig. 2D–F). The GC patients were divided into two groups (high versus low BEX4 expression) based on median value of BEX4 expression. Kaplan-Meier survival analysis demonstrated that the low BEX4 expression group had worse prognosis compared with the high BEX4 expression group ($P = .009$, Fig. 2G). Subgroup analysis revealed that the low BEX4 expression group had worse prognosis in tubular stomach adenocarcinoma (Fig. 2H) but not in diffuse type stomach adenocarcinoma (Fig. 2I), and stomach adenocarcinoma (Fig. 2J). The univariate analysis indicated that low BEX4 expression was associated with worse OS compared with high expression group (hazard ratio [HR] = 0.632, $P = .0215$). Other clinical variables, such as age, and TNM stage, also associated with worse OS ($P < .05$) (Table 2). To confirm the prognostic value of BEX4 expression, multivariate analysis was carried out. After adjusting for other risk factors, the multivariate Cox analysis revealed that BEX4 expression was independently associated with OS (HR = 0.627, 95%CI: 0.431–0.823, $P = .0201$), as well as age (HR = 1.049, 95%CI: 1.017–1.083, $P = .003$) and stage (HR = 1.865, 95%CI: 1.251–2.779,

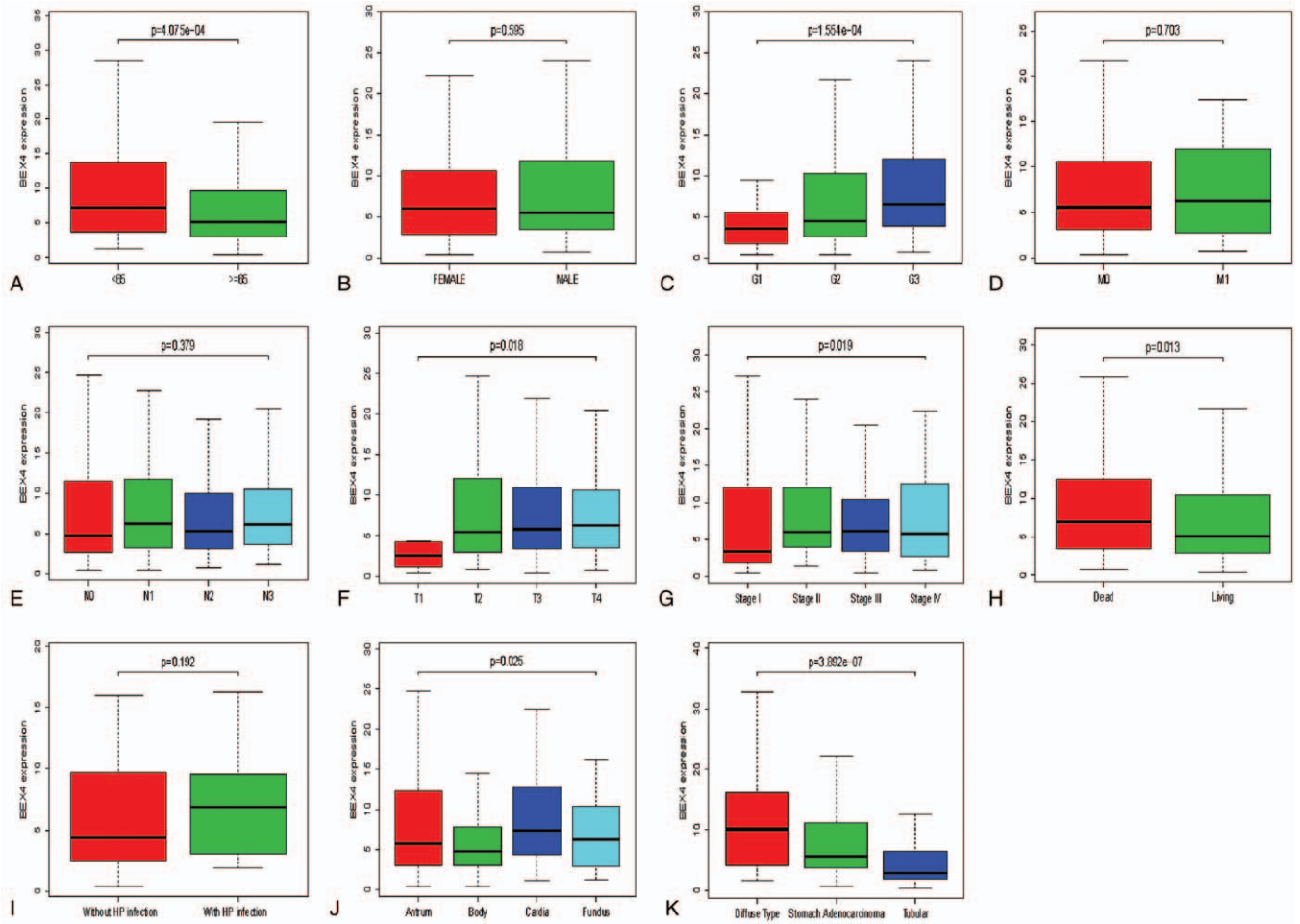


Figure 1. Association of BEX4 expression with clinical variables in patients with gastric cancer. BEX4 expression was compared between gastric cancer tissues and normal tissues in TCGA cohort according to (A) age, (B) gender, (C) grade, (D) M stage, (E) N stage, (F) T stage, (G) pathological stage, (H) patients survival status, (I) Helicobacter pylori infection, (J) cancer regions, and (K) cancer subtypes.

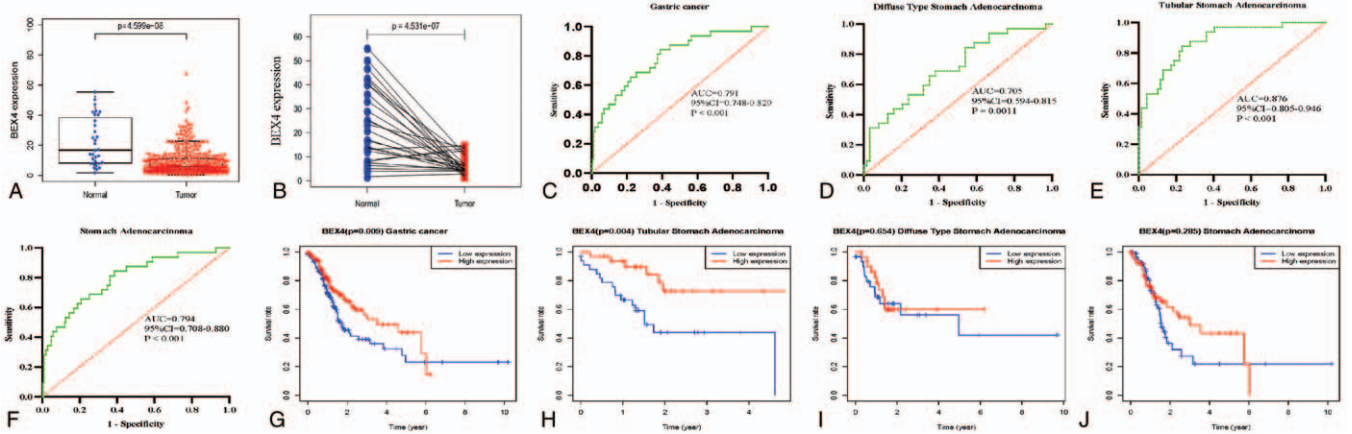


Figure 2. The expression patterns as well as diagnostic and prognostic value of BEX4 in gastric cancer. (A) BEX4 was obviously low expressed in cancer tissues compared to normal tissues ($P < .0001$); (B) BEX4 was expressed at lower levels in gastric cancer compared to 27 pairs of adjacent tissues ($P < .0001$); (C) Diagnosis value of BEX4 expression in normal gastric tissues and 375 gastric cancer tissues; The diagnostic performance of BEX4 in diffuse type stomach adenocarcinoma (D), stomach adenocarcinoma (E), and tubular stomach adenocarcinoma (F). (G) Impact of BEX4 expression on overall survival in gastric cancer patients in TCGA cohort; Kaplan-Meier survival analysis stratified by tubular stomach adenocarcinoma (H), diffuse type stomach adenocarcinoma (I), and stomach adenocarcinoma (J).

Table 1
logistic regression of BEX4 expression associated with clinical pathological characteristics.

Clinical Characteristics	Total (N)	Odds Ratio in BEX4 Expression	95%CI	<i>P</i> ^a
TNM stage (II vs I)	159	2.475	1.238-5.105	.0118
(III vs I)	198	2.266	1.165-4.554	.0181
(IV vs I)	86	1.954	0.815-4.764	.1351
T classification (T2 vs T1)	93	2.925	0.938-11.124	.081
(T3 vs T1)	184	3.534	1.195-12.951	.033
(T4 vs T1)	117	3.665	1.203-13.716	.0321
M classification (M1 vs M0)	350	1.296	0.572-3.004	.5344
N classification (N1 vs N0)	203	1.641	0.944-2.872	.0802
(N2 vs N0)	181	1.146	0.631-2.079	.654
(N3 vs N0)	180	1.464	0.807-2.672	.211
Age (≥65 vs <65)	368	0.583	0.383-0.884	.0115
Gender (Male vs Female)	368	0.909	0.594-1.393	.664
Helicobacter pylori infection (Yes vs No)	160	2.176	0.799-6.548	.14
Grade classification (G2 vs G1)	231	2.633	0.629-17.906	.232
(G3 vs G1)	228	5.376	1.310-36.176	.036
Cancer type (Diffuse vs Adenocarcinoma)	265	0.569	0.312-1.016	.006
(Tubular vs Adenocarcinoma)	132	0.251	0.119-0.512	.00018
Cancer regions (Cardia vs Body)	178	1.976	1.093-3.609	.0252
(Fundus vs Body)	133	1.612	0.779-3.358	.198
(Antrum vs Body)	221	1.518	0.883-2.626	.133

^a Statistically significant *P* values are given in bold, *P* < .05.

P = .002). Overall, all these reveal that BEX4 is an independent prognostic predictor of GC.

3.3. Validation in HPA and GEO databases

We checked BEX4 protein expression in multiple normal human and cancer tissues in HPA database. BEX4 protein expression was low in most normal human tissues (Fig. 3A). By examining BEX4 protein expression in cancerous tissues in the HPA, we also found that its expression varied substantially in different organs, among which the stomach presented low expression (Fig. 3B). Among 10 GC tissues examined, one case had medium to high staining, 4 cases had low staining and 5 cases not detected. Representative immunohistochemistry images of BEX4 staining were showed in Figure 3C–F.

To further validate the results from the TCGA cohort, we used GSE62254 as an external cohort to test the prognosis value and whether BEX4 remain an independent predictor of GC prognosis. Based on the median value of BEX4 expression in GSE62254 dataset, the GC patients were divided into high expression and low expression groups. As revealed by the Kaplan-Meier survival analysis in Figure 4A, the low BEX4

expression group also presented worse prognosis compared with the high BEX4 expression group (*P* < .0001). The univariate analysis indicated that low BEX4 expression group was associated with poor survival compared with high expression group (HR = 0.511, *P* < .001), as well as TNM stage and pathological stage (All *P* < .001, Fig. 4B). After adjusting for other risk factors, the multivariate Cox analysis confirmed the role of BEX4 expression as an independent prognostic predictor for OS in GC (HR = 0.647, 95%CI: 0.459–0.912, *P* = .013), as well as pathological stage (HR = 1.611, 95%CI: 1.072–2.421, *P* = .022, Fig. 4C). Therefore, all these results demonstrate that BEX4 is an independent prognostic predictor of GC.

3.4. GSEA identifies BEX4-related signaling pathways

To screen for the possible signaling pathways and mechanism that are differentially activated in GC, we performed GSEA between the high and low BEX4 expression datasets with data from the TCGA cohort. GSEA revealed significant differences in the enrichment of the MSigDB collection (h.all.v7.0.symbols.gmt). The most significantly enriched signaling pathways based on their normalized enrichment score were identified. As showed

Table 2
Univariate and multivariate analysis of the relationship of BEX4 expression with overall survival among gastric cancer patients.

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	<i>P</i> value	HR	95%CI	<i>P</i> value
Cancer regions	1.055	0.851-1.307	.623	1.055	0.837-1.329	.648
Cancer subtype	1.128	0.857-1.483	.391	1.004	0.741-1.359	.979
Helicobacter pylori infection	0.605	0.253-1.448	.259	0.536	0.210-1.365	.191
Age	1.039	1.009-1.071	.01	1.049	1.017-1.083	.003
Gender	1.634	0.892-2.995	.112	1.589	0.836-3.019	.157
Grade	1.352	0.840-2.177	.213	1.502	0.884-2.549	.133
Stage	1.672	1.157-2.417	.006	1.865	1.251-2.779	.002
BEX4 expression	0.632	0.420-0.844	.0215	0.627	0.431-0.823	.0201

BEX4 = brain-expressed X-linked 4; HR = hazard ratio; CI = confidence interval. Bold values indicate *P* < .05.

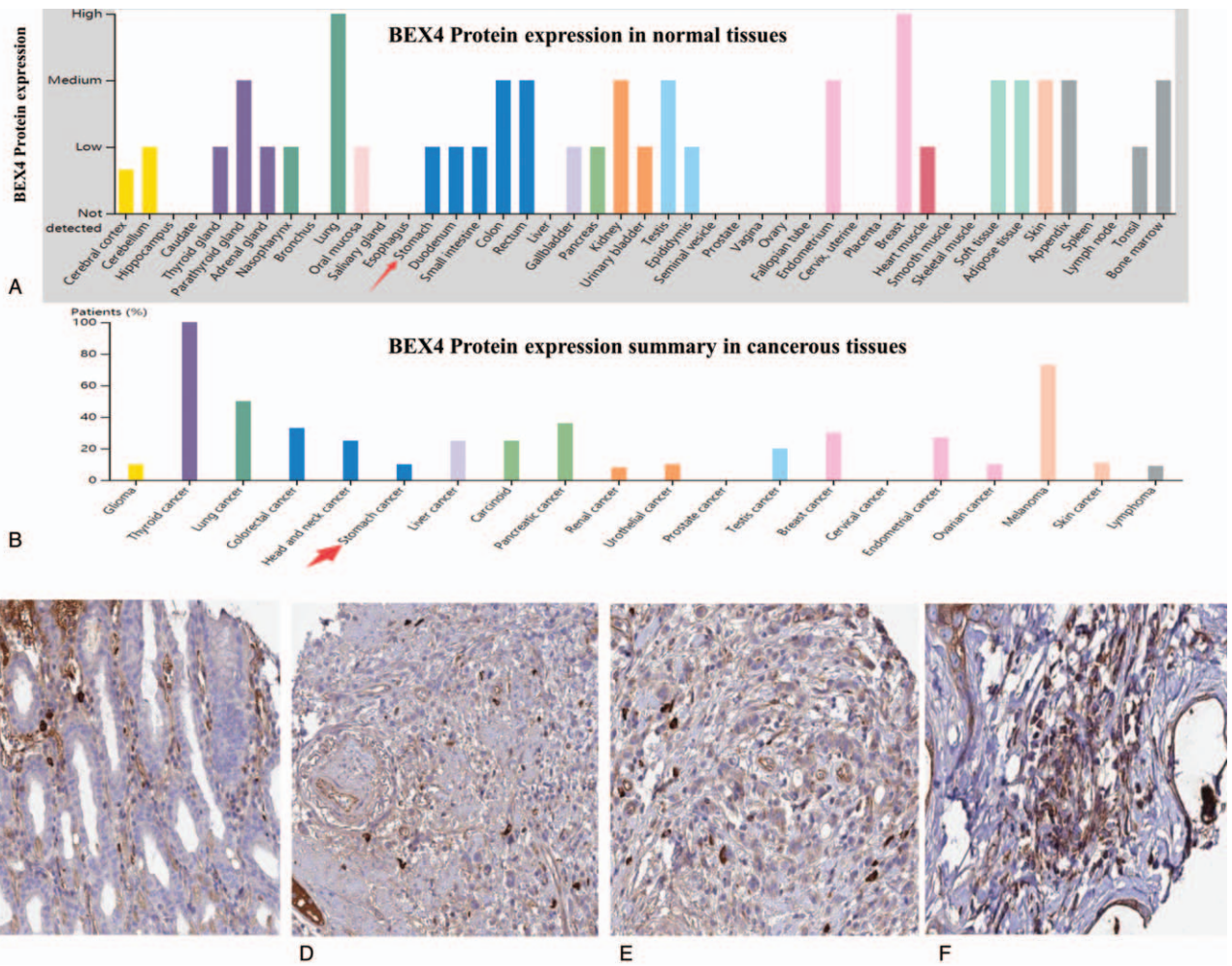


Figure 3. BEX4 expressions at protein level in human normal and cancer tissues. (A) The protein expression profiles of BEX4 in normal human tissues. (B) The protein expression profiles of BEX4 in human cancer tissues. (C) Representative IHC images of BEX4 expression in normal gastric tissues, and gastric cancer tissues using human protein atlas database (D, not detected; E, low staining, F, medium staining).

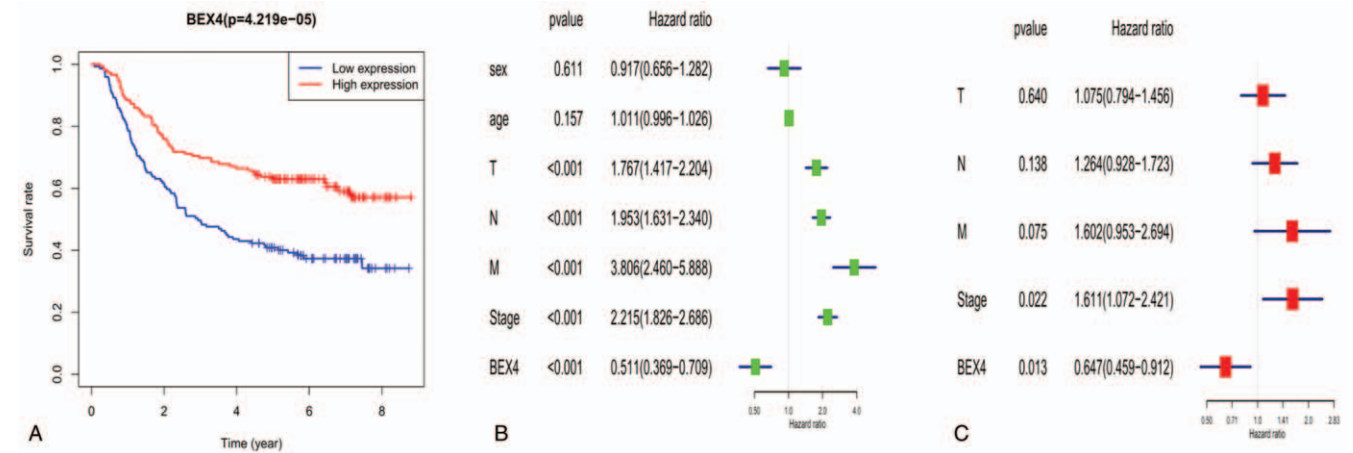


Figure 4. Validation the prognostic value of BEX expression in gastric cancer in GSE62254 dataset. (A) Low BEX4 expression was associated with a poor survival in gastric cancer patients in GSE62254 dataset ($P < .0001$). (B) Univariate analysis and (C) multivariate analysis of the correlation of BEX4 expression with overall survival among gastric cancer patients.

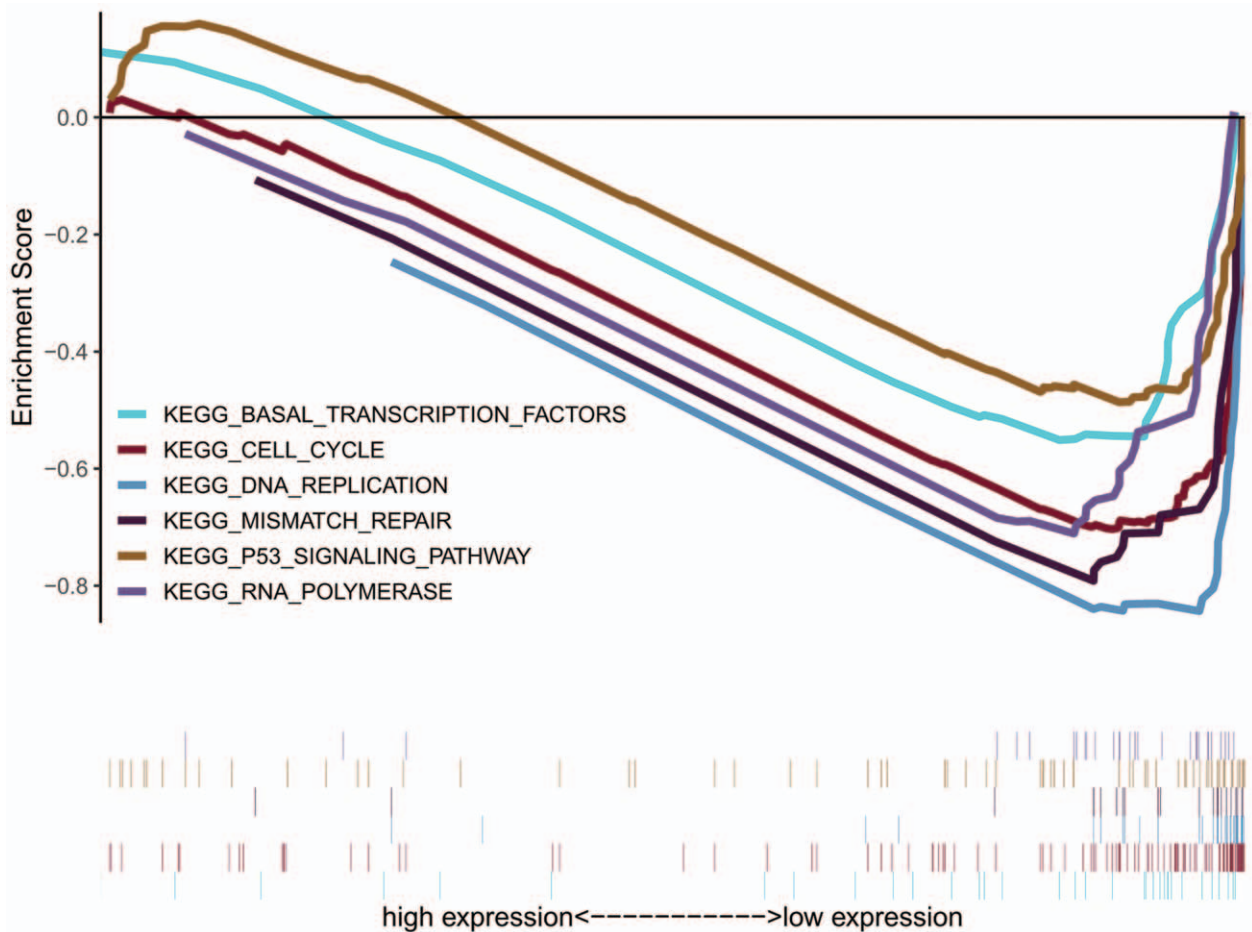


Figure 5. Enrichment plots from gene set enrichment analysis (GSEA). Basal transcription factors, DNA replication, RNA polymerase, mismatch repair, cell cycle, and P53 signaling pathway might be closely correlated with prognosis of gastric cancer.

in Figure 5, the expression of BEX4 was closely related to the basal transcription factors, DNA replication, RNA polymerase, mismatch repair, cell cycle, and P53 signaling pathway.

4. Discussion

The Brain-Expressed X-linked (BEX) family members consist of BEX1, BEX2, BEX3, BEX4 and BEX5. Unlike other members of BEX family, at present, little is known about the diagnostic and prognostic value of BEX4 in GC. Thus, we first examined the mRNA levels of BEX4 in GC tissues and compared with normal tissues. Recently, BEX4 was identified as an oncogene because its over-expression contributed to the proliferation and tumor growth potential by inducing oncogenic aneuploidy transformation.^[13] A recent study also confirmed that BEX4 was up-regulated in lung adenocarcinoma tissues and it accelerated lung adenocarcinoma cell proliferation.^[11] However, another study revealed that BEX4 functions as tumor suppressor by inhibiting proliferation and growth of oral squamous cell carcinoma. High BEX4 expression could suppress proliferation of oral squamous cell carcinoma in vitro, and reduced BEX4 contributes to the enhanced proliferative propensity of oral squamous cell carcinoma.^[12] In this study, using data from the TCGA, we identified that BEX4 was significantly expressed at lower level at

the mRNA and protein level in GC tissues compared to the adjacent normal tissues. We then analyzed the relationship between BEX4 mRNA expression and clinical parameters of GC. We found that BEX4 expression was also strongly associated with age, histologic grade, TNM stage, T stage, patient survival status, cancer subtype, and cancer regions. ROC analysis also confirmed the excellent diagnostic value of BEX4 expression in GC with AUC of 0.791. In addition, we also demonstrated that its under-expression was an independent indicator of worse survival, after adjustment of age, TNM stage, and pathological stage. Furthermore, we used GSE62254 to validate the independent indicator. A multivariate adjustment for other factors indicated that BEX4 expression remained an independent prognostic factors with an HR of 0.647 (95%CI: 0.459–0.912, $P = .013$) in the GSE62254 dataset. These findings suggest that BEX4 expression may be a novel tumor-suppressor for GC.

Furthermore, potential mechanisms underlying the effect of BEX4 expression on GC prognosis were analyzed by GSEA, and results revealed that basal transcription factors, DNA replication, RNA polymerase, mismatch repair, cell cycle, and P53 signaling pathway, correlate with prognostic of GC. Members of BEX family have been involved in regulating apoptosis in several human cancer cells and normal cells. BEX1 promotes imatinib-induced apoptosis by binding to and antagonizing BCL-2 in

human leukemic cell line K562.^[14] In breast cancer, BEX2 could mediate ceramide-induced apoptosis via protein phosphatase 2A.^[15] BEX4 overexpression presented a proliferative advantage to abnormal mitotic cells and protected them against spindle damage-induced apoptosis, and its expression enhances the generation of aneuploidy cells by reducing the apoptotic cell death.^[13,16] All these evidences revealed that BEX4 mainly involved in the cell cycle, DNA replication, and RNA polymerase process. P53 signaling pathway has been confirmed to play an important role in GC in many studies.^[17–19] Furthermore, it has reported that cyclins were associated with cell cycle and p53 signaling pathway in GC.^[18] P53 signaling pathway, cell cycle, DNA replication, and toll-like receptor signaling pathway were closely related to gastric adenocarcinoma.^[20] In our study, we identified P53 signaling pathway in GC prognosis, which is consist with previous studies.

To the best of our knowledge, the present study first identifies BEX4 not only as a useful biomarker for diagnose of GC, but also as a potential independent prognosis predictor for patients with GC. However, there were several limitations. First, the relative small number of patients included in the study is a limitation in this study, future work need to expend the sample size to verify this conclusion and subgroup about different Lauren type GC should be performed. Second, this study was based on bioinformatics analysis, more in vivo and in vitro studies should be performed in the future to elucidate why the under-expression of BEX4 is associated with poor prognosis in GC patients.

5. Conclusion

In summary, based on the analysis of TCGA and GEO databases, the current study was the first to demonstrate that BEX4 expression may be a potential diagnostic and independent prognostic molecular marker in GC. Furthermore, DNA replication, RNA polymerase, cell cycle, and P53 signaling pathway may be the key pathways regulated by BEX4 in GC.

Author contributions

Conceptualization: Chenhong Zhu, Deshuang Xiao.

Data curation: Chenhong Zhu.

Formal analysis: Chenhong Zhu.

Funding acquisition: Chenhong Zhu, Deshuang Xiao.

Investigation: Chenhong Zhu.

Methodology: Chenhong Zhu.

Project administration: Chenhong Zhu, Deshuang Xiao.

Resources: Chenhong Zhu.

Software: Chenhong Zhu.

Supervision: Chenhong Zhu, Deshuang Xiao.

Writing – original draft: Chenhong Zhu.

Writing – review & editing: Deshuang Xiao.

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