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RESEARCH ARTICLE

THE CLINICAL SIGNIFICANCE OF SOX9 GENE IN DIFFERENT CANCER TYPES: AN IN-SILICO ANALYSIS

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Abstract

One of the common problems in the pathogenesis of human cancer is characterized as the dysregulation of transcription factors. SOX9 is important as it is one of the critical transcription factors involved in various diseases, including cancer. In addition, SOX9 also acts as a proto-oncogene or tumor suppressor gene, depending on the cancer type. In this study, we aimed to reveal the mutation and expression status of the SOX9 transcription factor and the effect of this gene on the survival of patients with different cancer groups. The data sets for expression analysis and overall survival analysis were performed by the GEPIA database. Analysis of the mutation profile was performed by the cBio database. As a result, SOX9 gene expressions were significantly elevated in BLCA, CESC, CHOL, COAD, ESCA, GBM, KIRP, LGG, LIHC, LUSC, OV, PAAD, READ, SKCM, STAD, TGCT, THYM, UCEC and UCS in cancer tissues compared to that in normal tissues ($p<0.05$). According to overall survival (OS) analysis; the SOX9 gene has a significant relationship with OS in ACC, CESC, KIRC, LGG, and THYM (ACC p:0.0079, CESC p:0.038, KIRC p:0.051, LGG p:0.00055, THYM p:0.031). A total of 170 mutations in SOX9 were determined according to mutation analysis. Seventy-six of them were detected as driver mutations. The analysis shows that SOX9 expression status has a different effect in each cancer type, and although there is no significant mutation in the SOX9 gene in ACC cancer type, high expression of this gene is important for survival. Therefore, it is of great importance to analyze the epigenetic changes in the SOX9 gene in ACC cancer type. The analysis also indicates that the SOX9 gene is discriminatory for the survival of adrenocortical carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, renal clear cell carcinoma, brain low-grade glioma and thymoma cancer types.

Keywords

SOX9,
Transcription factor,
Tumorigenesis,
Mutation,
Gene expression

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Abbreviations

ACC: Adrenocortical carcinoma
BLCA: Bladder Urothelial Carcinom
BRCA: Breast invasive carcinoma
CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL: Cholangio carcinoma
COAD: Colon adenocarcinoma
DLBC: Lymphoid Neoplasm Diffuse Large B-cell Lymphoma
ESCA: Esophageal carcinoma
GBM: Glioblastoma multiforme
HNSC: Head and Neck squamous cell carcinoma
KICH: Kidney Chromophobe
KIRC: Kidney renal clear cell carcinoma
KIRP: Kidney renal papillary cell carcinoma
LAML: Acute Myeloid Leukemia
LGG: Brain Lower Grade Glioma
LIHC: Liver hepatocellular carcinoma
LUAD: Lung adenocarcinoma
LUSC: Lung squamous cell carcinoma
MESO: Mesothelioma
OV: Ovarian serous cystadenocarcinoma
PAAD: Pancreatic adenocarcinoma
PCPG: Pheochromocytoma and Paraganglioma
PRAD: Prostate adenocarcinoma
READ: Rectum adenocarcinoma
SARC: Sarcoma
SKCM: Skin Cutaneous Melanoma
STAD: Stomach adenocarcinoma
TGCT: Testicular Germ Cell Tumors
THYM: Thyroid carcinoma (THCA), Thymoma
UCEC: Uterine Corpus Endometrial Carcinoma
UCS: Uterine Carcinosarcoma
UVM: Uveal Melanoma

1. INTRODUCTION

Dysregulation of transcription factors, which are critical in many important processes such as cell survival, proliferation, repair of DNA damage, tissue differentiation, homeostasis, metabolism, and apoptosis, constitutes one of the important problems in cancer development [1]. It has been stated that about 20% of oncogenes are identified as transcription factors (TF) [2]. Regulation of target gene transcription by TFs is performed via binding to specific DNA sequences in the promoter and/or enhancer region [3]. Therefore, direct and indirect mechanisms affecting TF activity were of significance such as point mutations, gene amplification or deletion, chromosomal translocations, expressional changes, and non-coding DNA mutations [4].

Transcription factors are divided into two groups; master TFs and differential TFs. The sex-determining region Y (SRY) – related HMG-box genes (SOX) genes, which are known as a developmental transcription factor, were examined in the differential TFs group. The SOX family consists of more than 20 members that mediate DNA binding by a highly conserved high mobility group (HMG) domain [5].

SOX transcription factors are known as regulators of developmental, physiological, and pathological events [6]. Considered within the SOX E family, the SOX9 gene plays a key role in chondrocyte differentiation and skeletal development and is one of the important transcription factors involved in various diseases, including cancer [1,6]. It is stated that the SOX9 gene is mutated in 2.76% of all cancers [7]. Significant associations were found between this gene and cancer of the breast, prostate, renal, thyroid, central nervous system (CNS), and gastrointestinal [6, 8-12]. Furthermore, SOX9 acts as a proto-oncogene or tumor suppressor gene depending on the type of cancer and certain conditions [13]. This makes SOX9 fascinating for cancer research. For instance, studies have shown that while SOX9 acts as an oncogene in lung, glioma, ovarian cancer, parathyroid cancer, hepatocellular carcinoma, breast cancer, pancreatic cancer, prostate cancer, gastric cancer, oral squamous cell carcinoma, esophageal squamous cancer, renal cancer, urothelial cancer, it acts as a tumor suppressor in colorectal cancer and cervical cancer. In the case of melanoma, it acts as both an oncogene and a tumor suppressor [13]. Besides, SOX proteins are stated as key players in cancer cell stemness, drug resistance, proliferation, invasion, and metastasis [13, 14-17]. SOX9 is considered also a biomarker in which its upregulation is correlated with undesirable prognosis [17, 18]. Especially in some types of cancer such as cervical cancer, SOX9 plays like a double-edged sword. It is therefore important to analyze this gene in different types of cancer.

In this study, we aimed to examine the expression, survival, and mutation analysis of SOX9 gene in a broad perspective of different cancer types. For this purpose, the GEPIA database was used to reveal the expression levels between normal and cancer tissues and the significance of this gene in overall survival. Additionally, the cBio database was used to analyze the mutation profiles.

2. MATERIALS AND METHODS

2.1. Database Analysis

The gene expression profiling interactive analysis was used to analyze the mRNA levels of the SOX9 gene in normal tissues, and its related cancer types. The impact of the SOX9 gene on cancer patients' overall survival in thirty-three cancer was carried out in the data set of The Cancer Genome Atlas (TCGA). The web interface is easy to use and data analysis is done through the "Expression DIY" and "Survival" tabs on the main page. In case of the gene name of interest and data sets are entered from the "Expression on Box Plot" tab, the system calculates using log2 (transcripts per million+1) for log scale and creates a plot for Match TCGA normal and GTEx data. For survival analysis, a plot is created after giving the gene symbol to the "Gene" tab and selecting the data set. In the calculation of the Hazard ratio, selecting a Cox PH Model and the group cut-off value as median, quartile or custom is optional. In our analysis, the hazard ratio was calculated based on the Cox PH Model, and the group cut-off value was chosen as the median.

2.2. Gene Expression Profiling Interactive Analysis

GEPIA (http://gepia.cancer-pku.cn/) is an online database containing expression profiles of 9736 tumor samples and 8587 healthy samples. This interactive bioinformatics tool was developed to provide customizable analysis such as differential expression analysis in tumor or normal tissues, profiling by cancer types or pathological stages, patient survival analysis, similar gene detection, correlation analysis, and dimensionality reduction analysis. In-silico analysis was performed with 9498 tumor samples and 5540 healthy samples for expression analysis and 9473 tumor samples for survival data. The targeted gene, SOX9, expression analysis was performed for 31 cancer types having convenient data from the GEPIA database.

2.3. Survival Analysis

The analysis was performed with available Overall Survival (OS) patient data from the GEPIA database. Overall survival analysis based on a Log-rank test with a 95% confidence interval was performed to generate survival plots. Survival analysis according to the low and high mRNA expression levels of the study genes was performed via the web interface.

2.4. cBio Cancer Genomics Portal (cBioPortal) Analysis

cBio Cancer Genomics Portal (http://cbioportal.org) is an open-access bioinformatics tool that provides mutation data, copy number changes, microarray, and RNA sequencing-based m-RNA expression changes, DNA methylation values, protein and phosphoprotein levels with data from "The Cancer Genome Atlas (TCGA)". In all of the TCGA PanCancer Atlas studies; 32 projects were included in 10967 case studies. To comprehensively examine the mutations in the SOX9 gene, it was selected as the cancer type of interest from the web interface. For this purpose, comprehensive mutation profile analyses were performed using the features provided by the interface of the genes of interest using OncoPrint, Cancer Types Summary, and Mutation tools provided by cBioPortal.

2.5. Statistical Analysis

All statistical analyses were carried out on the GEPIA database. Kaplan-Meier analyses were conducted to estimate the OS rate of cancers. Low-high-expression groups were compared using the log-rank test. The p-values for the analyzes were calculated automatically by the database, and p-values below 0.05 were considered statistically significant.

3. RESULTS

3.1. Gene Expression Analysis of Selected Genes in GC

SOX9 gene expression was significantly high in BLCA, CESC, CHOL, COAD, ESCA, GBM, KIRP, LGG, LIHC, LUSC, OV, PAAD, READ, STAD, THYM, UCEC, UCS in cancer tissues compared to that in normal tissues ($p<0.05$). Conversely, SOX9 gene expression was high in SKCM and TGCT in normal tissues compared to that in cancer tissues ($p<0.05$) (Figure 1). Expression analysis of all cancer types were given in detail in Supplementary Figure 1.

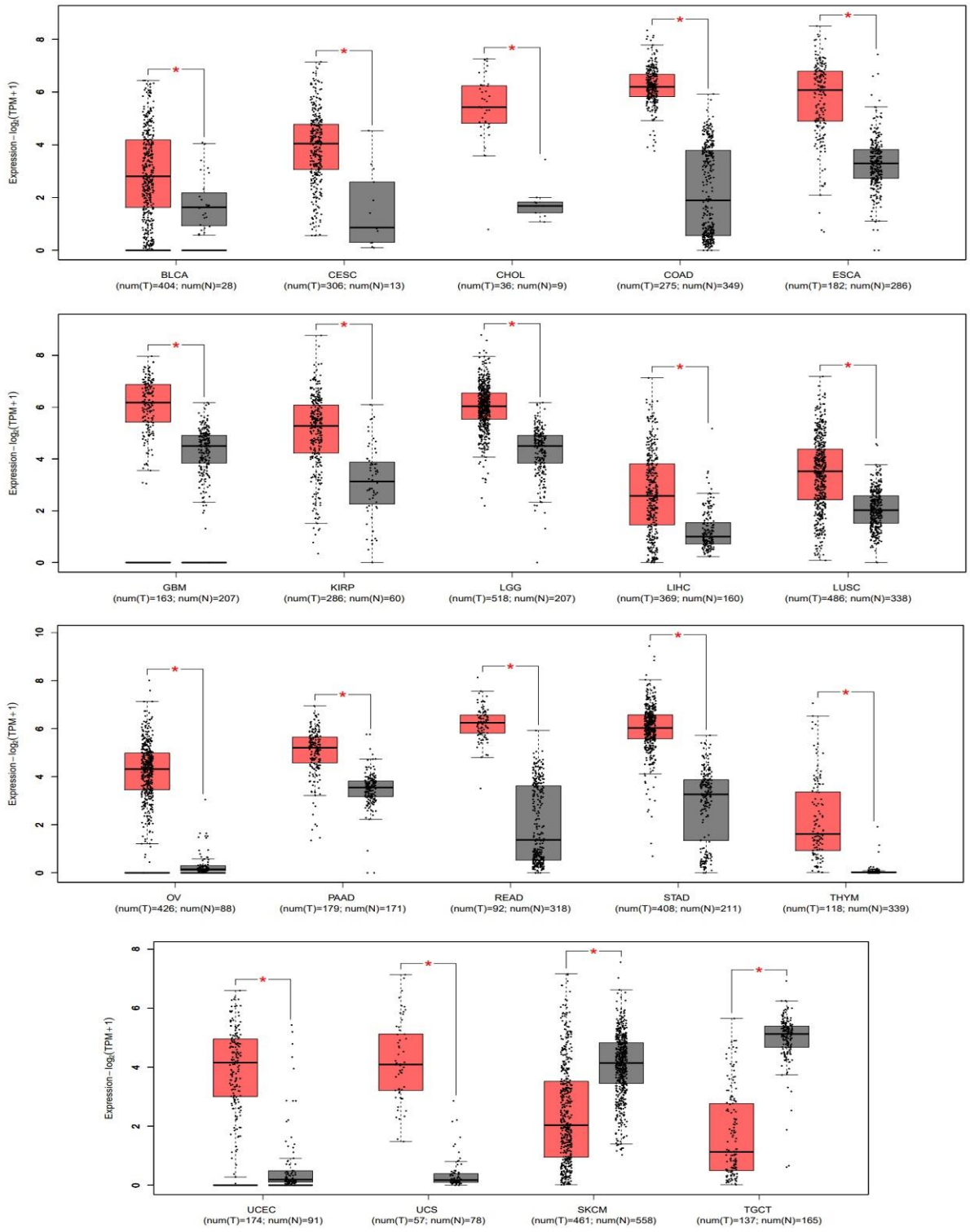

Figure 1. Comparative analysis of the tissue-specific differential expression of SOX9 gene using GEPIA (*indicates p<0.05). Red bar indicates tumor, grey bar indicates normal tissue

3.2. Survival Analysis of Selected Genes in GC

The significance level of the SOX9 gene in 33 different cancer types on OS is as follows; ACC p:0.0079, BLCA p:0.33, BRCA p:0.65, CESC p:0.038, CHOL p:0.78, COAD p:0.36, DLBC p:0.91, ESCA p:0.33,

GBM p:0.23, HNSC p:0.11, KICH p:0.45, KIRC p:0.051, KIRP p:0.9, LAML p:0.13, LGG p:0.00055, LIHC p:0.23, LUAD p:0.079, LUSC p:0.19, MESO p:0.31, OV p:0.66, PAAD p:0.33, PCPG p:0.92, PRAD p:0.6, READ p:0.44, SARC p:0.37, SKCM p:0.17, STAD p:0.31, TGCT p:0.45, THCA p:0.55, THYM p:0.031, UCEC p:0.76, UCS p:0.32, UVM p:0.16. According to the survival graphs, it was found that the SOX9 gene has a significant relationship with OS in ACC, CESC, KIRC, LGG, and THYM (Figure 2). Survival graphs of all cancer types were given in detail in Supplementary Figure 2.

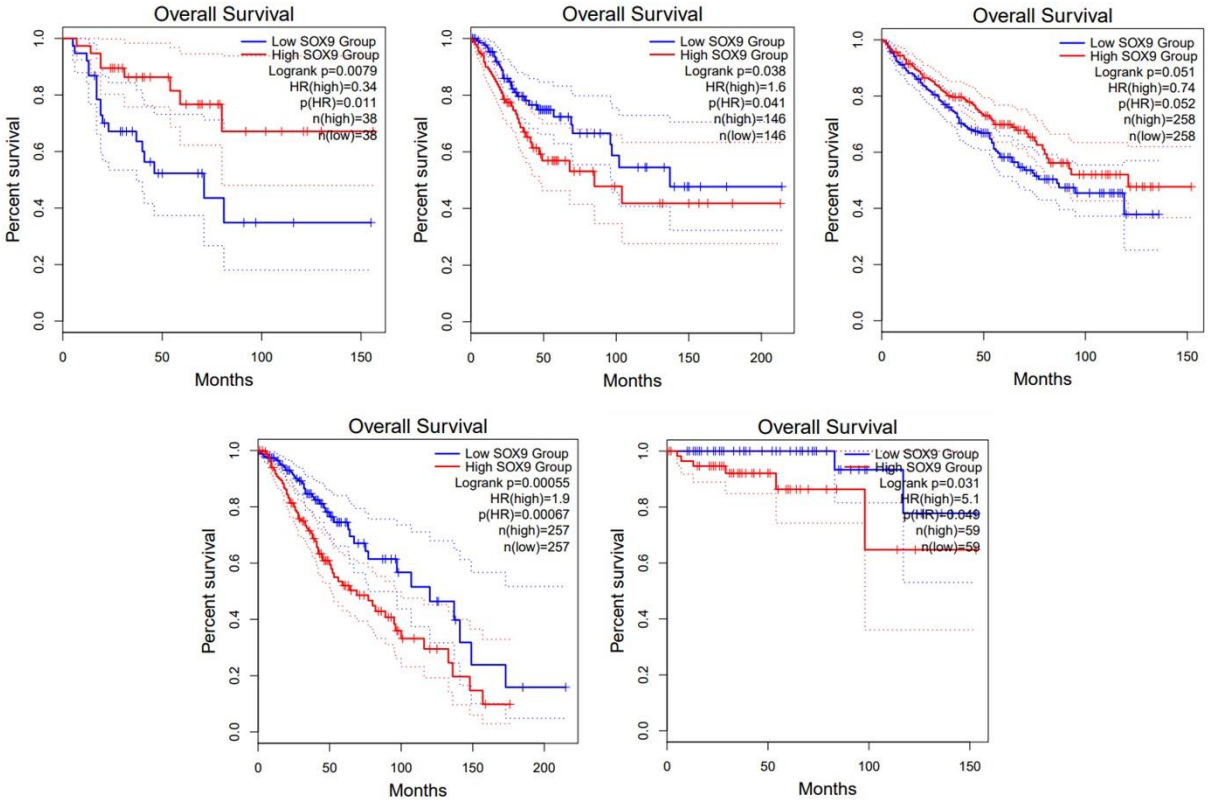

Figure 2. Overall survival analysis of the SOX9 gene in ACC, CESC, KIRC, LGG, THYM using GEPIA (*indicates p<0.05).

3.3. Results of Comprehensive SOX9 Mutation Analysis

Genome sequencing data of patients were analyzed via the cBioPortal interface, aiming to identify genetic changes in the SOX9 gene in the TGCA pan-cancer Atlas court, which consisted of a total of 10967 patient samples. A total of 170 mutations (89 missense mutations, 69 nonsense, 9 frameshifts, 3 splice region) were determined in the SOX9 gene. The features of these mutations are thoroughly listed in Table 1. Seventy-six of these mutations were detected as driver mutations. Deep deletion and gene amplifications were also detected from the whole 32 TCGA PanCancer Atlas studies. At least one of the above-mentioned mutations was detected in 2.9% of the patient group (Figure 3A). The localization of the mutations detected on the domains of the proteins belonging to the SOX9 gene in TCGA PanCancer Atlas cohorts is shown in Figure 3B. Colorectal adenocarcinoma has the highest mutation rate in terms of carrying SOX9 genetic anomaly in 32 different cancer types (Figure 3C). SOX9 mutation was not detected in Acute Myeloid Leukemia (TCGA, PanCancer Atlas) Adrenocortical Carcinoma (TCGA, PanCancer Atlas) Cholangiocarcinoma (TCGA, PanCancer Atlas) Diffuse Large B-Cell Lymphoma (TCGA, PanCancer Atlas) Kidney Chromophobe (TCGA, PanCancer Atlas) and Testicular Germ Cell Tumors (TCGA, PanCancer Atlas).

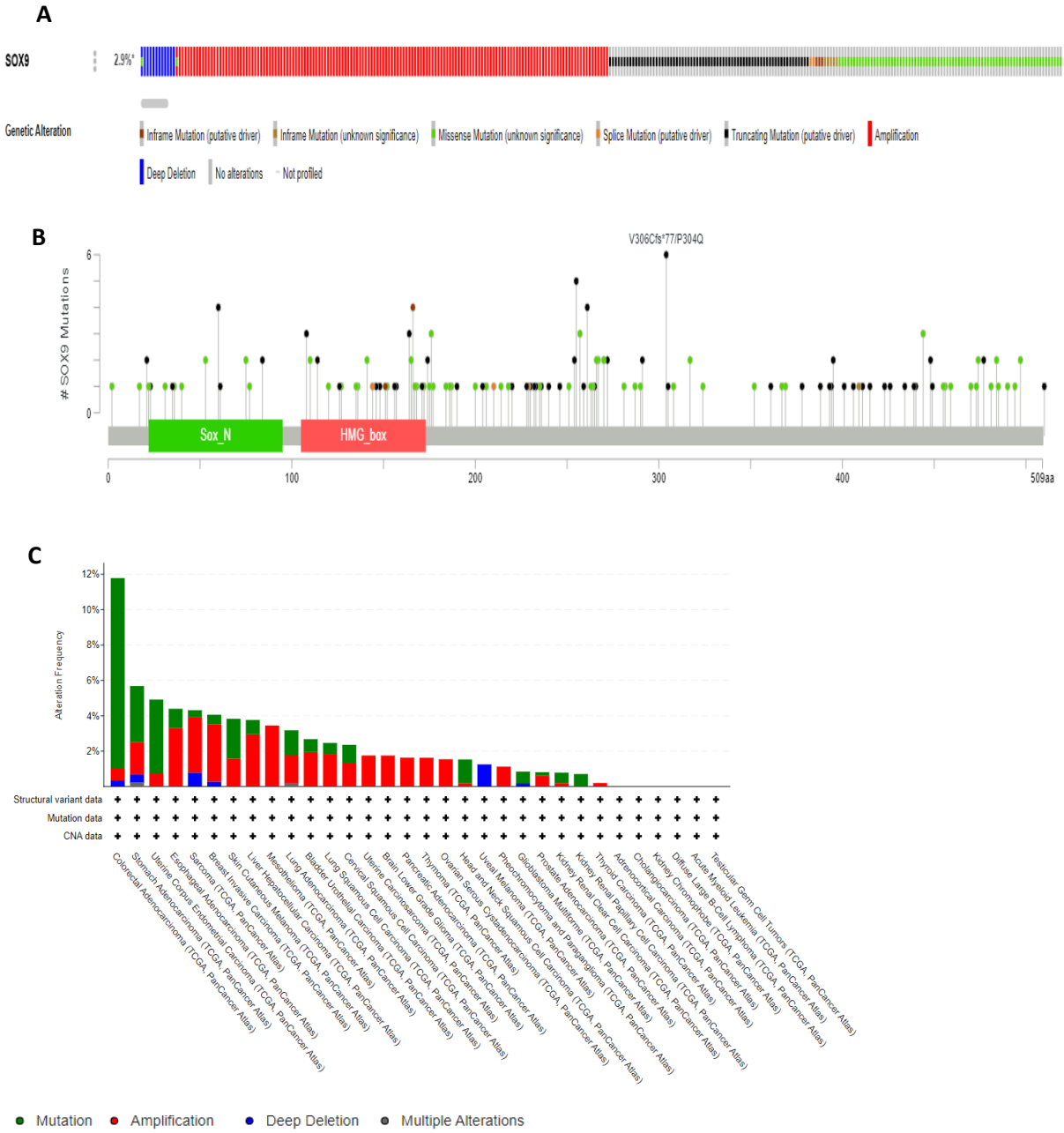

Figure 3. (A) Distribution of mutations in SOX9 gene in TCGA Pan Cancer cohorts from cBioPortal. Percentages of overall mutations for SOX9 gene is given on the left. **(B)** The lollipop graphic of domain architecture of the SOX9 protein and mutations detected in TCGA Pan Cancer Atlas cohorts. Human SOX9 s a polypeptide comprising 509 amino acids. SOX_N: Sox developmental protein N-terminal HMG_box: High-Mobility Group. **(C)** Distribution of SOX9 alterations across different cancer types and TCGA PanCancer studies.

4. DISCUSSION AND CONCLUSION

In the present analysis, SOX9 gene expression was found to have changed between cancer vs normal tissues in 61.29% (19 of 31) of investigated cancer types. SOX9 gene expression was significantly high in BLCA, CESC, CHOL, COAD, ESCA, GBM, KIRP, LGG, LIHC, LUSC, OV, PAAD, READ, STAD, THYM, UCEC, UCS in cancer tissues compared to that in normal tissues ($p<0.05$). The expression of

the SOX9 gene in SKCM and TGCT cancer types was found high in normal tissues compared to cancer tissues. Especially in OV, THYM, UCEC, and UCS cancer types, it is noteworthy that SOX9 gene expression is very low in normal tissues. Therefore, increased SOX9 gene expression in these four cancer types; ovarian cancer, thymoma, endometrial cancer, and uterine carcinosarcoma may have diagnostic value. According to the survival graphs of our analysis of the SOX9 gene in 33 different cancer types, a significant relationship with OS in ACC, CESC, KIRC, LGG, and THYM (ACC p:0.0079, CESC p:0.038, KIRC p:0.051, LGG p:0.00055, THYM p:0.031) was found. However, the points to be considered in the interpretation of this analysis are as follows: as high SOX9 expression increases survival in ACC and KIRC cancer types, low SOX9 expression provides higher survival in CESC, LGG, and THYM cancer types. Therefore, the therapeutic use of SOX9 expected to be different in each type of cancer. Besides, literature expresses SOX9 as double-edged sword in cervical cancer since SOX9 possesses both tumor-suppressor and tumor-promoting role [19-21]. In addition, examinig the results of the mutation analysis of the SOX9 gene of these cancer types (ACC, CESC, KIRC, LGG, THYM), which are important in terms of survival showed that the ACC cancer type does not have any mutation in the SOX9 gene. This is remarkable since there is no significance when normal tissue and cancerous tissue are compared for SOX9 gene expression in this cancer type, but in survival analysis, increased SOX9 gene expression indicates more survival. This suggests that epigenetic mechanisms may affect SOX9 expression in the ACC cancer type. In fact, in the review article by Ettaieb et al. examining the role of epigenetics in ACC diagnosis, prognosis and therapeutic strategies, CTNNB1 gene is referred as among the most altered genes by somatic mutations, DNA copy-number alterations and epigenetic silencing. It is also known that in ACC, the Wnt/β-catenin (CTNNB1) is frequently activated with CTNNB1 mutations and this leads to poor prognosis [22]. The article, which also drew attention to epigenetic modifications in CTNNB1, allowed us to examine the relationship between CTNNB1 and SOX9. Therewith we performed an analysis for CTNNB1 and SOX9 interaction via STRING, a database of functional protein association networks, and found that CTNNB1 and SOX9 genes interacted (Supplementary Figure 3). As the radical surgical resection is the only curable option and the prognostic stratification is extremely important to individualize adjuvant therapies, it will be meaningful to examine in detail the epigenetic alterations and interaction between CTNNB1 and SOX9 in understanding the pathogenesis of ACC. Mutation analyses of four other cancer types in terms of SOX9 mutations were as follows; CESC and KIRC cancer types have missense mutation and gene amplification, LGG and THYM cancer types have gene amplification. According to the localization of the mutations, it was detected that all investigated mutations in our mutational analyses were found in the HMG domain. As the HMG box domain alone carries out DNA binding, DNA bending, protein interactions, and nuclear import or export functions, mutations in this domain are important. Another important inference can be related to the localization of the mutations on the HMG domain: HMG domain comprises two nuclear localization signal (NLS) sequences; one is located at the N-terminus and contributes to the nuclear translocation of SOX9 by binding to calmodulin (NLS1) and one is located at the C-terminus and interacts with importin b to form a complex (NLS2) and a leucine-rich nuclear export signal (NES) sequence. NES sequence, located between the two NLS sequences and mediate the nuclear export of SOX9 [23]. NLS1 sequence is present between 105-121, the NES sequence is present between 134-147 and the NLS2 sequence is present between 179-182 [24]. As it was stated that NLS sequences and the NES sequence can be activated by different pathways, it can be important to investigate the mutations found in these regions [23]. In the result of analysis P108S, N110T, N110S, W115Gfs*136, V114L, and R120C mutations are in the range of NLS1 sequence signal, L135F, K141E, K141N, and X144_splice mutations are in the range of NES sequence signal (Supplementary Table 1).

In conclusion, as it is clearly seen in the analysis we performed, SOX9 expression status has different effect in each cancer type. It is noteworthy that the ACC cancer type does not have a significant mutation in the SOX9 gene although the high expression of this gene makes a significant difference in terms of survival. Therefore, analyzing epigenetic changes in the SOX9 gene in the ACC cancer type is of great importance. The analysis also points out that the SOX9 gene is distinctive for the survival of

adrenocortical carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, kidney renal clear cell carcinoma, brain lower grade glioma, and thymoma cancer types.

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CONFLICT OF INTEREST

The authors stated that there are no conflicts of interest regarding the publication of this article.

CRediT AUTHOR STATEMENT

Ethem Serhat Yavas: Investigation, Formal analysis, Writing, Visualization. **Sedef Hande Aktas:** Original draft, Writing, Supervision, Visualization, Conceptualization**. Göksel Efendioğlu:** Investigation, Formal analysis, Writing. **Dilara Fatma Akın:** Writing, Visualization, Conceptualization.

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