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Expression Profiles and Cerna Regulation Network of SOX Genes in Gastric Cancer

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1. Abstract

Aberrant expression of the SRY-related HMG-box (SOX) genes contributes to tumor development and progression. This research aimed to identify the regulation of the SOX genes in Gastric Cancer (GC). Expression profiles downloaded from The Cancer Genome Atlas (TCGA) were conducted to analyze the expression and function of the SOX genes. A competing endogenous RNAs (ceRNA) network mediated by the SOX genes was effectively constructed consisting of 64 lncRNAs, 29 miRNAs, and 11 SOX genes based on predicted miRNAs shared by lncRNAs and mRNAs using miRDB, TargetScan, miRTarBase, miRcode, and starBase v2.0. SOX9 was identified as a prognostic signature, which showed the usefulness of diagnosis and prognosis of GC by the receiver operating characteristic (ROC) and Kaplan-Meier curves. SOX9 was also shown specifically in GC and identified as highly expressed in the gastrointestinal tract. Gene Ontology (GO) enrichment analysis showed that SOX9 might influence the genes related to the pattern specification process, sodium ion homeostasis, and potassium ion transport, mainly including FEZF1, HOXC13, HOXC10, HOXC9, HOXA11, DPP6, ATP4B, CASQ2, KCNA1, ATP4A, and SFRP1. Furthermore, HOTAIR knockdown, miR-206-mimic transfection, the Cell Count Kit-8 (CCK-8) assay were performed to verify the function of HOTAIR/miR-206/SOX9 axis, which was identified in the ceRNA network analysis. HOTAIR could induce proliferation potentially by competitively binding miR-206/SOX9 axis in GC. These findings provide new clues with prognostic and therapeutic implications in gastric cancer and suggest that HOTAIR/miR-206/SOX9 might be a potential new strategy for therapeutic targeting of gastric cancer.

2. Introduction

Gastric cancer (GC) is one of the major issues of public health around the world. GC is also the most common malignant tumor in the digestive system. GC ranks third in the deaths of various cancer according to the American Cancer Society [1]. It is known that the early diagnosis rate of GC is low, the malignant degree is elevated, and the prognosis is poor. After all the treatments used in curative GC, the 5-year survival rate after surgical resection is still very low. This means GC is a serious threat to the health of people. Thus, searching for new biological targets in GC is indispensable.

The SOX (SRY-related HMG-box) gene family with HMG (High Mobility Group) domains subcomponent is A to H, and regulates the capacity to reprogram the cell fates by pioneering the epigenetic remodeling of the genome [2]. The SOX gene family is also an important transcriptional regulator that promotes tumorigenesis and development [3]. Studies have found abnormally expressed SOX genes in various kinds of tumors. SOX2 [4], SOX3 [5], SOX4 [6], SOX5 [7], and SOX9 [8], play as the role of pathological oncogenes, are significant highly expressed in skin squamous-cell carcinoma, gastric cancer, osteosarcoma, prostate cancer, and colorectal cancer. While SOX1 [9], SOX7 [10], SOX11 [11], and SOX17 [12], are expressed in low levels in cervical adenocarcinoma, breast cancer, hepatocellular carcinoma, cholangiocarcinoma, playing the role of tumor suppressor proteins.

MicroRNAs (miRNAs) play an important role in regulating genes associated with malignant biological behavior in cancer cells [13, 14]. The abnormal expression of long-chain non-coding RNA (lncRNA) is correlated with the occurrence and development of tumors and other diseases [15, 16]. miR-363 and miR-132 were identified inhibiting cell growth and metastasis in osteosarcoma cell lines possibly by downregulation of Sox4 [17, 18]. The study also found that miR-145 targets the *SOX11* 3'UTR to suppress the propagation and metastasis of endometrial cancer cells [19]. Up-regulation of miR-129-5p can reduce nerve injury and inflammatory response of Alzheimer's disease by down-regulating SOX6 [20]. On the other hand, the regulation of competing for endogenous RNAs (ceRNAs), which are transcripts that can regulate each other at the post-transcription level by competing for shared miRNAs, is involved in cancer initiation and progression [21, 22]. LncRNA could inhibit miRNA function, as "sponges" of natural miRNA, by competing with the binding of the microRNA response elements (MREs) in the complex [23, 24]. LncRNA UCA1 promoted cell proliferation and invasion and inhibited apoptosis by regulating SOX4 via miR129 in renal cell carcinoma, offering a promising therapeutic target and prognosis marker for patients [25]. LncRNA DANCR/miR-138/Sox4, a positive loop, was demonstrated that facilitating malignancy in non-small cell lung cancer [26]. However, the full role of SOX genes in GC remains unclear and fewer studies have been reported on SOX genes mediated ceRNA networks in GC.

In the present study, we conducted a multi-step analysis using various R language packages on clinical samples downloaded from The Cancer Genome Atlas (TCGA) database [27] to identify the differentially expressed SOX genes in the GC. The SOX genes mediated ceRNA network was established based on the lncRNA-miRNA-mRNA interaction. The receiver operating characteristic (ROC) curve and the Kaplan–Meier survival analysis were conducted to evaluate the diagnostic values of SOX genes for overall survival (OS). The biological functions enrichment analysis of the differentially expressed genes regulated by SOX9 was identified to investigate the downstream regulation role of SOX9. Furthermore, the HOTAIR/miR-206/SOX9 axis was investigated in GC cell lines.

3. Methods and Materials

3.1. Expression Profiles Information

The expression data and the corresponding clinical information from the patients with stomach adenocarcinoma (STAD) were obtained from the TCGA data portal (https://portal.gdc.cancer.gov/). The dataset included a total of 404 samples, consisting of 32 healthy and STAD samples (Table S1). LncRNA, miRNA, and mRNA expression profiles were obtained using the Data Transfer Tool. LncRNA and mRNA were quantified based on the Genome Research Project of ENCyclopedia of DNA Elements (GENCODE) (GRCh38) catalog (http://www.gencodegenes.org/). The transformed data (sense_overlapping, lincRNA, 3prime_overlapping_ncrna, processed_transcript, antisense and sense_intronic) were considered lncRNA.

3.2. Differential Expression Analysis

The differentially expressed genes (DEGs), lncRNAs (DELs), and miRNAs (DEMs) between GC tissues and non-tumor adjacent tissues of the TCGA dataset, were calculated using the limma package in R with its voom method [28]. Adjusted *P*-value<0.05, |log2 fold change (FC)|>1.5 for DEGs, >1.0 for DELs and DEMs, were set as cut-off criteria. Visualization of the identified DEGs, DEMs, and DELs including volcano plot and heatmap were performed with the "ggplot2" and "pheatmap" packages of R, respectively [29]. Then, the overlapped genes between DEGs and SOX genes using the VennDiagram package of R were identified as differentially expressed SOX genes [30].

3.3. Cerna Networks and Correlation Analysis

miRNA-mRNA interactions were obtained from the reliable online miRNA-target databases, including miRDB, TargetScan, miRTarBase, etc., using the "multiMiR" package in R (http://multimir.org/) [31]. LncRNA-miRNA interaction pairs were predicted using the online databases, miRcode (http://www.mircode.org/index.php) and starBase v2.0 (http://starbase.sysu.edu.cn/starbase2/) [32]. Then integrated with the miRNA-mRNA interactions to establish a dysregulated lncRNA-miRNA-mRNA ceRNA network and visualize using Cytoscape software [33]. Meanwhile, spearman's test was used to conduct the correlation analysis of the RNAs in the ceRNA network. The two-sided $P<0.05$ was considered statistically significant. Differentially expressed lncRNA HOTAIR and miRNA miR-206 associated with SOX9 were used for further study.

3.4. Survival Analysis and ROC Curves

To investigate the relationship between the expression of the genes and the overall survival (OS) in STAD patients, the expression profiles were normalized by log2 transformation. Survival analysis employed the minimum *P* value approach to finding the cut point in continuous gene expression measurement for dividing patients into high- and low-level groups. The hazard ratios (HRs) with 95% confidence intervals (CI) were also computed. Survival curves of the genes were evaluated and plotted using the Kaplan-Meier method and the Log-rank test by the "survival" and "survminer" packages in R (https://CRAN.R-project.org/package=survival). The Log-rank test was used to evaluate statistical significance with a cut-off criterion of $P < 0.05$. Then ROC curve analysis was performed to evaluate the sensitivity (true positive rate) and specificity (true negative rate) of SOX genes for STAD diagnosis by "survival ROC" packages in R. The area under the curve (AUC) was also calculated.

3.5. Functional Enrichment Analysis of SOX9 Associated Degs

To explore the regulatory role of the prognostic m^6A methylation-related genes on mRNA expression, the median value of their expression levels was applied as a cut-off to divide HCC samples into high- and low-level groups. Differentially expressed genes associated with

SOX9 were analyzed. Then, to better understand the biological functions of SOX9, Gene Ontology (GO) covering biological processes (BP), molecular functions (MF), and cellular components (CC) enrichment analyses of the DEGs regulated by SOX9 were performed [34]. The whole human genome was set as the background, and functional categories with adjusted $P<0.05$ were considered significant.

3.6. Cell Lines and Quantitative Real-Time PCR (Qrt-PCR)

The GC cell lines (AGS, NCI-N87, MKN45, and HGC-27) were obtained from the Institute of Cell Biology, Chinese Academy of Sciences, Shanghai. Cells were cultured in RPMI1460 medium (Gibco, USA) containing 10% FBS (Gibco, USA), which incubated in 5% CO_2 at 37^{0}C. Total RNAs were extracted by using Trizol Reagent (Invitrogen, CN) based on the manufacturer's instruction. Next, 2μg RNA was used to synthesize cDNA by using the Advantage RT-for-PCR Kit (Clontech) according to the manufacturer's protocol. cDNA was diluted and used to perform *q*RT-PCR with HiScript® II One Step *q*RT-PCR SYBR® Green Kit (Takara, Japan). GADPH and U6 were used as the internal control for mRNA and miRNA, respectively. Expression data was calculated using the $2^{-\Delta\Delta Ct}$ method.

3.7. RNA Interference

HOTAIR siRNA, miR-206-mimic, and miR-497-inhibitor were purchased from Biomics Biotech Company, China. The details were showed in Table S2. All miRNAs were diluted according to the introduction and transferred into cells with EntansterTM-R4000 (Engreen Biosystem Co, Ltd).

Table S1: Clinical information of GC patients in TCGA datasets

event (%)	ALIVE	185 (58.9)
	DEAD	128 (40.8)
	NOT REPORTED	1 (0.3)
stage (%)	I	50 (15.9)
	II	98 (31.2)
	III	133 (42.4)
	IV	33 (10.5)
M (%)	M0	279 (88.9)
	M1	22 (7.0)
	MX	13 (4.1)
N (%)	N0	102 (32.5)
	N1	80 (25.5)
	N2	69 (22.0)
	N3	63 (20.1)
T (%)	T1	18 (5.7)
	T2	67 (21.3)
	T3	148 (47.1)
	T4	81 (25.8)
EvsA (%)	Advanced	264 (84.1)
	Early	50 (15.9)
AGE (%)	<=60	103 (33.0)
	>60	209 (67.0)
Gender (%)	FEMALE	119 (37.9)
	MALE	195 (62.1)
Race (%)	asian	64 (20.4)
	black or african american	9 (2.9)
	not reported	48 (15.3)
	white	193 (61.5)

Table S2: The sequence of primers in this study

Name of primers	sequence
SOX9 F	5'-TGCTCGGGCACTTATTGG-3'
SOX9 R	5'-TCCTCAGGCTTTGCGATTT-3'
HOTAIR F	5'-CAGTGGGGAACTCTGACTCG-3'
HOTAIR R	5'-GTGCCTGGTGCTCTCTTACC-3'
GADPH F	5'-CTTCGCTTCGCTATCATCGACG-3'
GADPH R	5'-TCGAACGTCTAGCGAAGCTA-3'
si-HOTAIR1:	5'-AAAUCCAGAACCCUCUGACAUUUGC-3'
si-HOTAIR2:	5'-UUAAGUCUAGGAAUCAGCACGAAGC-3'
si-HOTAIR3:	5'-CAUAUUAUAGAGUUGCUCUGUGCUG-3'

3.8. Luciferase Reporter Assays

MKN45 cells were seeded and cultured on 24-well plates. For luciferase reporter assays, HOTAIR, HOTAIR -mut, 3'UTR of SOX9, 3'UTR of SOX9 mut was co-transfected with miR-206-mimic or miR-497-inhibitor into MKN45 cells. After 48 hours of transfection, the luciferase activities were detected by the Dual Luciferase Reporter Assay (Promega Corporation, Madison, USA). The luciferase activity was analyzed according to the manufacturer's protocol and was presented as the relative luciferase activity. Each assay was performed three times.

3.9. CCK-8 Assay

The function of SOX9 in GC cell proliferation was detected by using the CCK-8 assay (GlpBio, USA). The cells were seeded in 96-well plates with 1×10^5/well. The cells were transfected with si-HOTAIR, and then the absorbance of each group was detected after adding CCK-8 using a fluorescence microplate reader (Berthold Technologies, Germany) at 450 nm. Student's *t*-test was used to examine the differences. Each experiment was performed in triplicate. $P < 0.05$ represented a significant difference.

4. Results

4.1. Identification of Degs, Dems, Dels in Gastric Cancer

A total of 1990 DEGs, 129 DEMs, and 1529 DELs between GC and normal samples were obtained. Among them, 889 mRNAs, 63 miRNAs, and 909 lncRNAs were significantly upregulated; while 1101 mRNAs, 66 miRNAs, and 620 lncRNAs were significantly downregulated, respectively (Figure 1). To screen the SOX genes that were differentially expressed in GC and normal tissues, venn diagram analysis was used to obtain the overlapping genes between DEGs and the SOX genes. In total 19 SOX genes, four genes, SOX9, SOX4, SOX14, and SOX11, were identified up-regulated. Meanwhile, three genes were down-regulated including SOX21, SOX2, and SOX15. (Figure 2).

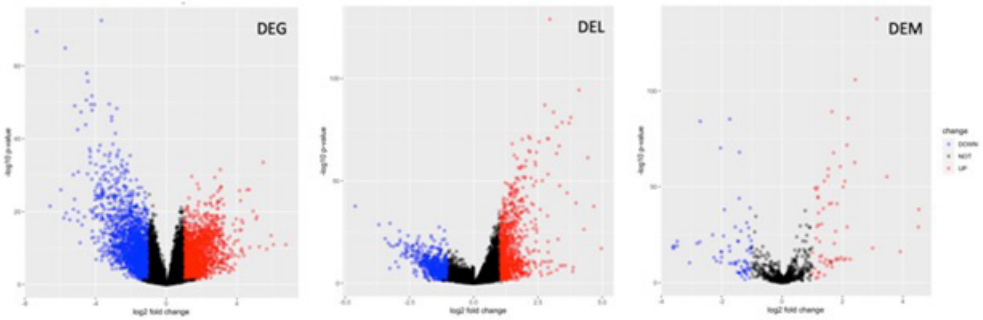

Figure 1: Volcano plots of DEGs, DELs, and DEMs between STAD and normal tissues for datasets from TCGA. X-axis: log2 fold change; Y-axis: -log 10 (p-value) for each gene; vertical-dotted lines: log2 fold change ≥1.5 or ≤-1.5 (DEGs), log2 fold change ≥1 or ≤-1 (DEMs and DELs); horizontal-dotted line: the significance cut off (adjusted p-value=0.05). the red dot represents u-regulated genes, and the blue dot represents down-regulated genes.

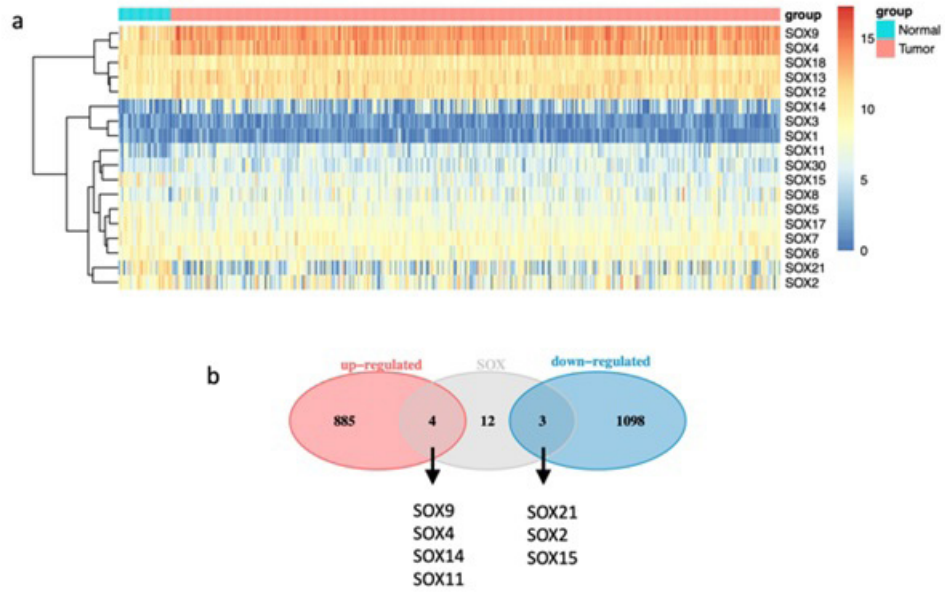

Figure 2: Differential expression of SOX family genes between STAD and normal tissues for datasets from TCGA. (a) Gene expression heat map of SOX family genes. (b) Venn diagrams of the overlapping genes between SOX genes with up-regulated DEGs and down-regulated DEGs, respectively.

4.2. ceRNA Network

To better understand the biological regulation roles of the SOX genes, we constructed the dysregulated ceRNA network based on the lncRNA-miRNA-mRNA interactions. The regulatory relationship between 580 miRNAs and 19 SOX genes was found using the "multiMiR" package in R (Table S3), 66 of these miRNAs were differentially expressed in GC tissues compared with normal tissues. Then, 64 lncRNAs were predicted to interact with 66 DEMs using the online databases, miRcode and starBase v2.0 (Table S4). Finally, integrated the relationship of miRNAs and mRNAs, miRNAs and lncRNAs, a ceRNA network consisting of 64 lncRNAs, 29 miRNAs, and 11 SOX genes were constructed (Figure 3a; Table S5). In addition, we calculated the connection degree of each gene by analyzing the topological structure to clarify its importance in the ceRNA network. SOX genes (SOX11, SOX4, and SOX9), lncRNAs (XIST, KCNQ1OT1, and NEAT1), and miRNAs (miR-20a, miR-129-2, miR-145) were considered the most important genes among the lncRNAs, miRNAs, and mRNAs, respectively (Figure 3b).

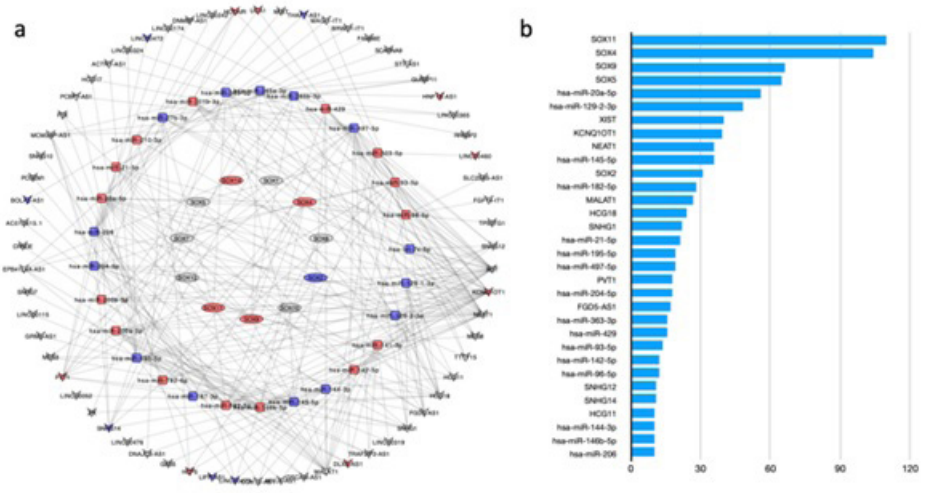

Figure 3: ceRNA networks of IncRNAs, miRNAs, and SOX genes. (a) Allow indicates IncRNA, rectangle indicates miRNA, and oval indicates SOX gene. The red color represents up-regulated gene, the purple color represents down-regulated gene, and the grey color represents non-significant gene. (b) the connection degree of each gene in the ceRNA network.

Table S3: miRNAs interact with SOX family genes retrieved from the databases.

database	mature_mirna_acc	mature_mirna_id	target_symbol	target_entrez	target_ensembl
mirecords	MIMAT0000765	hsa-miR-335-5p	SOX4	6659	ENSG00000124766
mirecords	MIMAT0000076	hsa-miR-21-5p	SOX5	6660	ENSG00000134532
mirecords	MIMAT0000265	hsa-miR-204-5p	SOX4	6659	ENSG00000124766
mirecords	MIMAT0000242	hsa-miR-129-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000765	hsa-miR-335-5p	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0003319	hsa-miR-649	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0027380	hsa-miR-6739-3p	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0019717	hsa-miR-4652-3p	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0022978	hsa-miR-4743-3p	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0003241	hsa-miR-576-5p	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0019760	hsa-miR-4677-5p	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0028222	hsa-miR-7156-5p	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0016903	hsa-miR-4273	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0028228	hsa-miR-7159-5p	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0015066	hsa-miR-3065-5p	SOX1	6656	ENSG00000182968
mirtarbase	MIMAT0000437	hsa-miR-145-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0000445	hsa-miR-126-3p	SOX2	6657	ENSG00000181449

mirtarbase	MIMAT0002868	hsa-miR-522-3p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0000255	hsa-miR-34a-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0004676	hsa-miR-34b-3p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0000686	hsa-miR-34c-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0000431	hsa-miR-140-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0001536	hsa-miR-429	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0000424	hsa-miR-128-3p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0000421	hsa-miR-122-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0000076	hsa-miR-21-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0004692	hsa-miR-340-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0003294	hsa-miR-625-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0003308	hsa-miR-638	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0005826	hsa-miR-1181	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0000449	hsa-miR-146a-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0004687	hsa-miR-371a-5p	SOX2	6657	ENSG00000181449
mirtarbase		hsa-miR-375	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0004909	hsa-miR-450b-5p	SOX2	6657	ENSG00000181449
mirtarbase	MIMAT0000083	hsa-miR-26b-5p	SOX3	6658	ENSG00000134595
mirtarbase	MIMAT0003235	hsa-miR-570-3p	SOX3	6658	ENSG00000134595
mirtarbase	MIMAT0026736	hsa-miR-548e-5p	SOX3	6658	ENSG00000134595
mirtarbase	MIMAT0004512	hsa-miR-100-3p	SOX3	6658	ENSG00000134595
mirtarbase	MIMAT0022268	hsa-miR-548as-3p	SOX3	6658	ENSG00000134595
mirtarbase	MIMAT0000765	hsa-miR-335-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000242	hsa-miR-129-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000440	hsa-miR-191-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0004605	hsa-miR-129-2-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000265	hsa-miR-204-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000430	hsa-miR-138-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0004697	hsa-miR-151a-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0004692	hsa-miR-340-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000420	hsa-miR-30b-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000096	hsa-miR-98-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000244	hsa-miR-30c-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000070	hsa-miR-17-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0004494	hsa-miR-21-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0005904	hsa-miR-1253	SOX4	6659	ENSG00000124766
mirtarbase		hsa-miR-3591-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0027669	hsa-miR-6884-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0018073	hsa-miR-3653-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0018078	hsa-miR-3658	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0003285	hsa-miR-548c-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0019043	hsa-miR-2392	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0018951	hsa-miR-4435	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0023707	hsa-miR-6082	SOX4	6659	ENSG00000124766

mirtarbase	MIMAT0004548	hsa-miR-129-1-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0004552	hsa-miR-139-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0016904	hsa-miR-4276	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0018943	hsa-miR-4428	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0019774	hsa-miR-4687-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0027459	hsa-miR-6779-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0027606	hsa-miR-6853-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0027673	hsa-miR-6886-3p	SOX4	6659	ENSG00000124766
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mirtarbase	MIMAT0000087	hsa-miR-30a-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000245	hsa-miR-30d-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000692	hsa-miR-30e-5p	SOX4	6659	ENSG00000124766
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mirtarbase	MIMAT0019070	hsa-miR-4531	SOX4	6659	ENSG00000124766
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mirtarbase	MIMAT0019982	hsa-miR-4802-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0019002	hsa-miR-4475	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000073	hsa-miR-19a-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000074	hsa-miR-19b-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000075	hsa-miR-20a-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000093	hsa-miR-93-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000103	hsa-miR-106a-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0031890	hsa-miR-203a-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000425	hsa-miR-130a-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000680	hsa-miR-106b-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0002890	hsa-miR-299-5p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000688	hsa-miR-301a-3p	SOX4	6659	ENSG00000124766
mirtarbase	MIMAT0000691	hsa-miR-130b-3p	SOX4	6659	ENSG00000124766
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tarbase	MIMAT0000682	hsa-miR-200a-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0001620	hsa-miR-200a-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000265	hsa-miR-204-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004493	hsa-miR-20a-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000075	hsa-miR-20a-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004494	hsa-miR-21-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004569	hsa-miR-222-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019952	hsa-miR-2467-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000082	hsa-miR-26a-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000083	hsa-miR-26b-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000084	hsa-miR-27a-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000419	hsa-miR-27b-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000690	hsa-miR-296-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000086	hsa-miR-29a-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004515	hsa-miR-29b-2-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000100	hsa-miR-29b-3p	SOX11	6664	ENSG00000176887

tarbase	MIMAT0000681	hsa-miR-29c-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0022696	hsa-miR-301a-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0015378	hsa-miR-3065-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019201	hsa-miR-3127-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004504	hsa-miR-31-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0015056	hsa-miR-3179	SOX11	6664	ENSG00000176887
tarbase	MIMAT0015058	hsa-miR-3180-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004505	hsa-miR-32-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000762	hsa-miR-324-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000761	hsa-miR-324-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000090	hsa-miR-32-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000756	hsa-miR-326	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004701	hsa-miR-338-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000764	hsa-miR-339-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004506	hsa-miR-33a-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000773	hsa-miR-346	SOX11	6664	ENSG00000176887
tarbase	MIMAT0017994	hsa-miR-3615	SOX11	6664	ENSG00000176887
tarbase	MIMAT0017999	hsa-miR-3619-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0018113	hsa-miR-3685	SOX11	6664	ENSG00000176887
tarbase	MIMAT0018205	hsa-miR-3928-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0018206	hsa-miR-3929	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004748	hsa-miR-423-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0001341	hsa-miR-424-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0016888	hsa-miR-4326	SOX11	6664	ENSG00000176887
tarbase	MIMAT0001545	hsa-miR-450a-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019058	hsa-miR-4521	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019061	hsa-miR-4523	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019064	hsa-miR-4525	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019772	hsa-miR-4685-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019805	hsa-miR-4705	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019873	hsa-miR-4742-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019966	hsa-miR-4793-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0002807	hsa-miR-491-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004768	hsa-miR-497-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0002820	hsa-miR-497-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004772	hsa-miR-499a-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0002870	hsa-miR-499a-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0021044	hsa-miR-5010-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0021086	hsa-miR-5094	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004780	hsa-miR-532-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003165	hsa-miR-545-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0019079	hsa-miR-548an	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003254	hsa-miR-548b-3p	SOX11	6664	ENSG00000176887

tarbase	MIMAT0005919	hsa-miR-548o-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003257	hsa-miR-550a-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0022275	hsa-miR-5581-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003225	hsa-miR-561-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003244	hsa-miR-579-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004801	hsa-miR-590-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003260	hsa-miR-592	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004804	hsa-miR-615-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003284	hsa-miR-616-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004807	hsa-miR-624-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004808	hsa-miR-625-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003294	hsa-miR-625-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003298	hsa-miR-629-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003311	hsa-miR-641	SOX11	6664	ENSG00000176887
tarbase	MIMAT0022711	hsa-miR-660-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000252	hsa-miR-7-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0003888	hsa-miR-766-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004949	hsa-miR-877-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004978	hsa-miR-935	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000442	hsa-miR-9-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004983	hsa-miR-940	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004985	hsa-miR-942-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0004605	hsa-miR-129-2-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000426	hsa-miR-132-3p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000449	hsa-miR-146a-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000268	hsa-miR-211-5p	SOX11	6664	ENSG00000176887
tarbase	MIMAT0000065	hsa-let-7d-5p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000098	hsa-miR-100-5p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0009196	hsa-miR-103a-2-5p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000443	hsa-miR-125a-5p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000423	hsa-miR-125b-5p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0022726	hsa-miR-1306-5p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000425	hsa-miR-130a-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0004612	hsa-miR-186-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000072	hsa-miR-18a-5p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0002819	hsa-miR-193b-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000226	hsa-miR-196a-5p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000073	hsa-miR-19a-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000086	hsa-miR-29a-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000100	hsa-miR-29b-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000681	hsa-miR-29c-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000688	hsa-miR-301a-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000750	hsa-miR-340-3p	SOX12	6666	ENSG00000177732

tarbase		hsa-miR-375	SOX12	6666	ENSG00000177732
tarbase	MIMAT0004780	hsa-miR-532-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0003276	hsa-miR-608	SOX12	6666	ENSG00000177732
tarbase	MIMAT0004985	hsa-miR-942-5p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0019776	hsa-miR-1343-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000279	hsa-miR-222-3p	SOX12	6666	ENSG00000177732
tarbase	MIMAT0000062	hsa-let-7a-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000421	hsa-miR-122-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000445	hsa-miR-126-3p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000444	hsa-miR-126-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000424	hsa-miR-128-3p	SOX2	6657	ENSG00000181449
tarbase		hsa-miR-137	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000437	hsa-miR-145-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000259	hsa-miR-182-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000076	hsa-miR-21-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000091	hsa-miR-33a-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0003308	hsa-miR-638	SOX2	6657	ENSG00000181449
tarbase		hsa-miR-320a	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000703	hsa-miR-361-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0019799	hsa-miR-4701-3p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000104	hsa-miR-107	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000685	hsa-miR-34b-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0001536	hsa-miR-429	SOX2	6657	ENSG00000181449
tarbase	MIMAT0004903	hsa-miR-300	SOX2	6657	ENSG00000181449
tarbase	MIMAT0022697	hsa-miR-382-3p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0004954	hsa-miR-543	SOX2	6657	ENSG00000181449
tarbase	MIMAT0004678	hsa-miR-99b-3p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000727	hsa-miR-374a-5p	SOX2	6657	ENSG00000181449
tarbase	MIMAT0000646	hsa-miR-155-5p	SOX1	6656	ENSG00000182968
tarbase	MIMAT0000765	hsa-miR-335-5p	SOX1	6656	ENSG00000182968
tarbase	MIMAT0000449	hsa-miR-146a-5p	SOX1	6656	ENSG00000182968
tarbase	MIMAT0000460	hsa-miR-194-5p	SOX1	6656	ENSG00000182968
tarbase	MIMAT0000318	hsa-miR-200b-3p	SOX1	6656	ENSG00000182968
tarbase	MIMAT0000084	hsa-miR-27a-3p	SOX1	6656	ENSG00000182968
tarbase	MIMAT0000684	hsa-miR-302a-3p	SOX1	6656	ENSG00000182968
tarbase	MIMAT0000062	hsa-let-7a-5p	SOX18	54345	ENSG00000203883
tarbase	MIMAT0004493	hsa-miR-20a-3p	SOX18	54345	ENSG00000203883
tarbase	MIMAT0000080	hsa-miR-24-3p	SOX18	54345	ENSG00000203883
tarbase	MIMAT0000765	hsa-miR-335-5p	SOX18	54345	ENSG00000203883
tarbase	MIMAT0000422	hsa-miR-124-3p	SOX18	54345	ENSG00000203883
tarbase	MIMAT0002830	hsa-miR-520f-3p	SOX18	54345	ENSG00000203883
tarbase	MIMAT0000726	hsa-miR-373-3p	SOX18	54345	ENSG00000203883
tarbase	MIMAT0000684	hsa-miR-302a-3p	SOX18	54345	ENSG00000203883

Table S4: lncRNAs interact with miRNAs retrieved from the databases.

miRNAname	geneName	geneType
hsa-let-7c-5p	SNHG12	antisense
hsa-let-7c-5p	KCNQ1OT1	antisense
hsa-let-7c-5p	NEAT1	lincRNA
hsa-let-7c-5p	MEG8	lincRNA
hsa-let-7c-5p	XIST	lincRNA
hsa-let-7c-5p	TTTY15	lincRNA
hsa-miR-129-1-3p	SNHG12	antisense
hsa-miR-129-1-3p	FGD5-AS1	antisense
hsa-miR-129-1-3p	HCG11	lincRNA
hsa-miR-129-1-3p	HCG18	antisense
hsa-miR-129-1-3p	KCNQ1OT1	antisense
hsa-miR-129-1-3p	SNHG1	processed_transcript
hsa-miR-129-1-3p	NEAT1	lincRNA
hsa-miR-129-1-3p	XIST	lincRNA
hsa-miR-129-2-3p	SNHG12	antisense
hsa-miR-129-2-3p	FGD5-AS1	antisense
hsa-miR-129-2-3p	HCG11	lincRNA
hsa-miR-129-2-3p	HCG18	antisense
hsa-miR-129-2-3p	KCNQ1OT1	antisense
hsa-miR-129-2-3p	SNHG1	processed_transcript
hsa-miR-129-2-3p	NEAT1	lincRNA
hsa-miR-129-2-3p	XIST	lincRNA
hsa-miR-141-3p	MYLK-AS1	antisense
hsa-miR-141-3p	TRAF3IP2-AS1	antisense
hsa-miR-141-3p	DLX6-AS1	antisense
hsa-miR-141-3p	KCNQ1OT1	antisense
hsa-miR-141-3p	NEAT1	lincRNA
hsa-miR-141-3p	MALAT1	lincRNA
hsa-miR-141-3p	DSCAM-AS1	antisense
hsa-miR-141-3p	LINC00319	lincRNA
hsa-miR-141-3p	XIST	lincRNA
hsa-miR-142-5p	FGD5-AS1	antisense
hsa-miR-142-5p	HCG18	antisense
hsa-miR-142-5p	LINC00473	lincRNA
hsa-miR-142-5p	KCNQ1OT1	antisense
hsa-miR-142-5p	NEAT1	lincRNA
hsa-miR-142-5p	COX10-AS1	processed_transcript
hsa-miR-144-3p	GAS5	processed_transcript
hsa-miR-144-3p	LIFR-AS1	antisense
hsa-miR-144-3p	HCG11	lincRNA
hsa-miR-144-3p	HCP5	sense_overlapping
hsa-miR-144-3p	LINC00476	lincRNA
hsa-miR-144-3p	NEAT1	lincRNA
hsa-miR-144-3p	MALAT1	lincRNA
hsa-miR-144-3p	DNAJC3-AS1	lincRNA
hsa-miR-144-3p	SNHG14	processed_transcript
hsa-miR-144-3p	XIST	lincRNA
hsa-miR-145-5p	HCG18	antisense
hsa-miR-145-5p	PVT1	lincRNA
hsa-miR-145-5p	KCNQ1OT1	antisense
hsa-miR-145-5p	SNHG1	processed_transcript
hsa-miR-145-5p	MALAT1	lincRNA
hsa-miR-145-5p	GRM5-AS1	antisense
hsa-miR-145-5p	MEG3	lincRNA
hsa-miR-145-5p	LINC00052	lincRNA
hsa-miR-145-5p	JPX	lincRNA
hsa-miR-146b-5p	LINC00115	lincRNA
hsa-miR-146b-5p	EPB41L4A-AS1	lincRNA
hsa-miR-146b-5p	HCG18	antisense
hsa-miR-146b-5p	SNHG7	antisense
hsa-miR-146b-5p	KCNQ1OT1	antisense
hsa-miR-146b-5p	NEAT1	lincRNA
hsa-miR-146b-5p	MALAT1	lincRNA
hsa-miR-146b-5p	CRNDE	lincRNA
hsa-miR-146b-5p	AC012615.1	lincRNA

hsa-miR-146b-5p	XIST	lincRNA
hsa-miR-182-5p	BOLA3-AS1	antisense
hsa-miR-182-5p	PCGEM1	lincRNA
hsa-miR-182-5p	KCNQ1OT1	antisense
hsa-miR-182-5p	SNHG1	processed_transcript
hsa-miR-182-5p	NEAT1	lincRNA
hsa-miR-182-5p	SNHG10	antisense
hsa-miR-182-5p	XIST	lincRNA
hsa-miR-187-3p	PVT1	lincRNA
hsa-miR-187-3p	KCNQ1OT1	antisense
hsa-miR-187-3p	MCM3AP-AS1	antisense
hsa-miR-192-5p	KCNQ1OT1	antisense
hsa-miR-192-5p	XIST	lincRNA
hsa-miR-192-5p	FTX	lincRNA
hsa-miR-195-5p	SNHG12	antisense
hsa-miR-195-5p	PCBP1-AS1	processed_transcript
hsa-miR-195-5p	FGD5-AS1	antisense
hsa-miR-195-5p	EPB41L4A-AS1	lincRNA
hsa-miR-195-5p	HCG18	antisense
hsa-miR-195-5p	HCG17	lincRNA
hsa-miR-195-5p	TRAF3IP2-AS1	antisense
hsa-miR-195-5p	LINC00473	lincRNA
hsa-miR-195-5p	DLX6-AS1	antisense
hsa-miR-195-5p	PVT1	lincRNA
hsa-miR-195-5p	KCNQ1OT1	antisense
hsa-miR-195-5p	SNHG1	processed_transcript
hsa-miR-195-5p	NEAT1	lincRNA
hsa-miR-195-5p	ACTN1-AS1	antisense
hsa-miR-195-5p	MEG3	lincRNA
hsa-miR-195-5p	MEG8	lincRNA
hsa-miR-195-5p	LINC00324	lincRNA
hsa-miR-195-5p	MCM3AP-AS1	antisense
hsa-miR-195-5p	XIST	lincRNA
hsa-miR-200a-3p	MYLK-AS1	antisense
hsa-miR-200a-3p	TRAF3IP2-AS1	antisense
hsa-miR-200a-3p	DLX6-AS1	antisense
hsa-miR-200a-3p	KCNQ1OT1	antisense
hsa-miR-200a-3p	NEAT1	lincRNA
hsa-miR-200a-3p	MALAT1	lincRNA
hsa-miR-200a-3p	DSCAM-AS1	antisense
hsa-miR-200a-3p	LINC00319	lincRNA
hsa-miR-200a-3p	XIST	lincRNA
hsa-miR-200b-3p	KCNQ1OT1	antisense
hsa-miR-200b-3p	NEAT1	lincRNA
hsa-miR-200b-3p	MALAT1	lincRNA
hsa-miR-200b-3p	MCM3AP-AS1	antisense
hsa-miR-200b-3p	XIST	lincRNA
hsa-miR-204-5p	HCG11	lincRNA
hsa-miR-204-5p	LINC00472	lincRNA
hsa-miR-204-5p	KCNQ1OT1	antisense
hsa-miR-204-5p	SNHG1	processed_transcript
hsa-miR-204-5p	NEAT1	lincRNA
hsa-miR-204-5p	MALAT1	lincRNA
hsa-miR-204-5p	DSCAM-AS1	antisense
hsa-miR-204-5p	MCM3AP-AS1	antisense
hsa-miR-204-5p	XIST	lincRNA
hsa-miR-206	LINC00242	lincRNA
hsa-miR-206	LINC00174	processed_transcript
hsa-miR-206	DNMBP-AS1	antisense
hsa-miR-206	NEAT1	lincRNA
hsa-miR-206	MALAT1	lincRNA
hsa-miR-206	HOTAIR	antisense
hsa-miR-206	SNHG14	processed_transcript
hsa-miR-206	COX10-AS1	processed_transcript
hsa-miR-206	UCA1	lincRNA
hsa-miR-206	MIAT	lincRNA
hsa-miR-20a-5p	FGD5-AS1	antisense
hsa-miR-20a-5p	MAGI1-IT1	sense_intronic

hsa-miR-20a-5p	EPB41L4A-AS1	lincRNA
hsa-miR-20a-5p	HCG18	antisense
hsa-miR-20a-5p	HCP5	sense_overlapping
hsa-miR-20a-5p	PVT1	lincRNA
hsa-miR-20a-5p	KCNQ1OT1	antisense
hsa-miR-20a-5p	NEAT1	lincRNA
hsa-miR-20a-5p	MALAT1	lincRNA
hsa-miR-20a-5p	HOTAIR	antisense
hsa-miR-20a-5p	SNHG14	processed_transcript
hsa-miR-20a-5p	THAP7-AS1	antisense
hsa-miR-20a-5p	XIST	lincRNA
hsa-miR-20a-5p	TTTY15	lincRNA
hsa-miR-21-5p	FAM66E	lincRNA
hsa-miR-21-5p	PVT1	lincRNA
hsa-miR-21-5p	SNHG1	processed_transcript
hsa-miR-21-5p	MALAT1	lincRNA
hsa-miR-21-5p	BRWD1-IT1	sense_overlapping
hsa-miR-21-5p	XIST	lincRNA
hsa-miR-21-5p	FTX	lincRNA
hsa-miR-210-3p	LINC00473	lincRNA
hsa-miR-210-3p	SCARNA9	antisense
hsa-miR-27b-3p	HCP5	sense_overlapping
hsa-miR-27b-3p	ST7-AS1	antisense
hsa-miR-27b-3p	PVT1	lincRNA
hsa-miR-27b-3p	KCNQ1OT1	antisense
hsa-miR-27b-3p	NEAT1	lincRNA
hsa-miR-27b-3p	DNAJC3-AS1	lincRNA
hsa-miR-27b-3p	GUSBP11	processed_transcript
hsa-miR-27b-3p	XIST	lincRNA
hsa-miR-301b-3p	BOLA3-AS1	antisense
hsa-miR-301b-3p	FGD5-AS1	antisense
hsa-miR-301b-3p	HCG18	antisense
hsa-miR-301b-3p	KCNQ1OT1	antisense
hsa-miR-301b-3p	NEAT1	lincRNA
hsa-miR-301b-3p	HOTAIR	antisense
hsa-miR-301b-3p	MCM3AP-AS1	antisense
hsa-miR-301b-3p	XIST	lincRNA
hsa-miR-363-3p	KCNQ1OT1	antisense
hsa-miR-363-3p	MALAT1	lincRNA
hsa-miR-363-3p	HNF1A-AS1	processed_transcript
hsa-miR-363-3p	LINC00365	lincRNA
hsa-miR-363-3p	MEG8	lincRNA
hsa-miR-363-3p	SNHG14	processed_transcript
hsa-miR-363-3p	XIST	lincRNA
hsa-miR-363-3p	JPX	lincRNA
hsa-miR-365a-3p	HCG18	antisense
hsa-miR-365a-3p	PVT1	lincRNA
hsa-miR-365a-3p	NEAT1	lincRNA
hsa-miR-365a-3p	SNHG14	processed_transcript
hsa-miR-365a-3p	GUSBP11	processed_transcript
hsa-miR-365a-3p	XIST	lincRNA
hsa-miR-365b-3p	HCG18	antisense
hsa-miR-365b-3p	PVT1	lincRNA
hsa-miR-365b-3p	NEAT1	lincRNA
hsa-miR-365b-3p	SNHG14	processed_transcript
hsa-miR-365b-3p	GUSBP11	processed_transcript
hsa-miR-365b-3p	XIST	lincRNA
hsa-miR-429	LINC00174	processed_transcript
hsa-miR-429	KCNQ1OT1	antisense
hsa-miR-429	NEAT1	lincRNA
hsa-miR-429	MALAT1	lincRNA
hsa-miR-429	LINC00365	lincRNA
hsa-miR-429	RRN3P2	processed_transcript
hsa-miR-429	MCM3AP-AS1	antisense
hsa-miR-429	XIST	lincRNA
hsa-miR-497-5p	SNHG12	antisense
hsa-miR-497-5p	PCBP1-AS1	processed_transcript
hsa-miR-497-5p	FGD5-AS1	antisense

hsa-miR-497-5p	EPB41L4A-AS1	lincRNA
hsa-miR-497-5p	HCG18	antisense
hsa-miR-497-5p	HCG17	lincRNA
hsa-miR-497-5p	TRAF3IP2-AS1	antisense
hsa-miR-497-5p	LINC00473	lincRNA
hsa-miR-497-5p	DLX6-AS1	antisense
hsa-miR-497-5p	PVT1	lincRNA
hsa-miR-497-5p	KCNQ1OT1	antisense
hsa-miR-497-5p	SNHG1	processed_transcript
hsa-miR-497-5p	NEAT1	lincRNA
hsa-miR-497-5p	ACTN1-AS1	antisense
hsa-miR-497-5p	MEG3	lincRNA
hsa-miR-497-5p	MEG8	lincRNA
hsa-miR-497-5p	LINC00324	lincRNA
hsa-miR-497-5p	MCM3AP-AS1	antisense
hsa-miR-497-5p	XIST	lincRNA
hsa-miR-503-5p	SNHG12	antisense
hsa-miR-503-5p	NEAT1	lincRNA
hsa-miR-503-5p	MALAT1	lincRNA
hsa-miR-503-5p	LINC00460	lincRNA
hsa-miR-503-5p	COX10-AS1	processed_transcript
hsa-miR-93-5p	FGD5-AS1	antisense
hsa-miR-93-5p	MAGI1-IT1	sense_intronic
hsa-miR-93-5p	EPB41L4A-AS1	lincRNA
hsa-miR-93-5p	HCG18	antisense
hsa-miR-93-5p	HCP5	sense_overlapping
hsa-miR-93-5p	PVT1	lincRNA
hsa-miR-93-5p	KCNQ1OT1	antisense
hsa-miR-93-5p	NEAT1	lincRNA
hsa-miR-93-5p	MALAT1	lincRNA
hsa-miR-93-5p	HOTAIR	antisense
hsa-miR-93-5p	SNHG14	processed_transcript
hsa-miR-93-5p	THAP7-AS1	antisense
hsa-miR-93-5p	XIST	lincRNA
hsa-miR-93-5p	TTTY15	lincRNA
hsa-miR-96-5p	TP53TG1	lincRNA
hsa-miR-96-5p	MALAT1	lincRNA
hsa-miR-96-5p	FGF14-IT1	sense_intronic
hsa-miR-96-5p	UCA1	lincRNA
hsa-miR-96-5p	XIST	lincRNA
hsa-miR-96-5p	SLC25A5-AS1	processed_transcript

Table S5: The interactions of lncRNA, miRNA, and SOX family genes in the ceRNA network in GC.

lncRNA	miRNA	mRNA
SNHG12	hsa-let-7c-5p	SOX4
XIST	hsa-let-7c-5p	SOX4
KCNQ1OT1	hsa-let-7c-5p	SOX4
NEAT1	hsa-let-7c-5p	SOX4
MEG8	hsa-let-7c-5p	SOX4
TTTY15	hsa-let-7c-5p	SOX4
HCG11	hsa-miR-129-1-3p	SOX4
SNHG12	hsa-miR-129-1-3p	SOX4
KCNQ1OT1	hsa-miR-129-1-3p	SOX4
NEAT1	hsa-miR-129-1-3p	SOX4
HCG18	hsa-miR-129-1-3p	SOX4
XIST	hsa-miR-129-1-3p	SOX4
FGD5-AS1	hsa-miR-129-1-3p	SOX4
SNHG1	hsa-miR-129-1-3p	SOX4
HCG11	hsa-miR-129-2-3p	SOX4
SNHG12	hsa-miR-129-2-3p	SOX4
HCG18	hsa-miR-129-2-3p	SOX4
SNHG1	hsa-miR-129-2-3p	SOX4
FGD5-AS1	hsa-miR-129-2-3p	SOX4
NEAT1	hsa-miR-129-2-3p	SOX4
KCNQ1OT1	hsa-miR-129-2-3p	SOX4
XIST	hsa-miR-129-2-3p	SOX4
HCG11	hsa-miR-129-2-3p	SOX14

SNHG12	hsa-miR-129-2-3p	SOX14
HCG18	hsa-miR-129-2-3p	SOX14
SNHG1	hsa-miR-129-2-3p	SOX14
FGD5-AS1	hsa-miR-129-2-3p	SOX14
NEAT1	hsa-miR-129-2-3p	SOX14
KCNQ1OT1	hsa-miR-129-2-3p	SOX14
XIST	hsa-miR-129-2-3p	SOX14
HCG11	hsa-miR-129-2-3p	SOX5
SNHG12	hsa-miR-129-2-3p	SOX5
HCG18	hsa-miR-129-2-3p	SOX5
SNHG1	hsa-miR-129-2-3p	SOX5
FGD5-AS1	hsa-miR-129-2-3p	SOX5
NEAT1	hsa-miR-129-2-3p	SOX5
KCNQ1OT1	hsa-miR-129-2-3p	SOX5
XIST	hsa-miR-129-2-3p	SOX5
HCG11	hsa-miR-129-2-3p	SOX7
SNHG12	hsa-miR-129-2-3p	SOX7
HCG18	hsa-miR-129-2-3p	SOX7
SNHG1	hsa-miR-129-2-3p	SOX7
FGD5-AS1	hsa-miR-129-2-3p	SOX7
NEAT1	hsa-miR-129-2-3p	SOX7
KCNQ1OT1	hsa-miR-129-2-3p	SOX7
XIST	hsa-miR-129-2-3p	SOX7
HCG11	hsa-miR-129-2-3p	SOX13
SNHG12	hsa-miR-129-2-3p	SOX13
HCG18	hsa-miR-129-2-3p	SOX13
SNHG1	hsa-miR-129-2-3p	SOX13
FGD5-AS1	hsa-miR-129-2-3p	SOX13
NEAT1	hsa-miR-129-2-3p	SOX13
KCNQ1OT1	hsa-miR-129-2-3p	SOX13
XIST	hsa-miR-129-2-3p	SOX13
HCG11	hsa-miR-129-2-3p	SOX11
SNHG12	hsa-miR-129-2-3p	SOX11
HCG18	hsa-miR-129-2-3p	SOX11
SNHG1	hsa-miR-129-2-3p	SOX11
FGD5-AS1	hsa-miR-129-2-3p	SOX11
NEAT1	hsa-miR-129-2-3p	SOX11
KCNQ1OT1	hsa-miR-129-2-3p	SOX11
XIST	hsa-miR-129-2-3p	SOX11
KCNQ1OT1	hsa-miR-141-3p	SOX11
LINC00319	hsa-miR-141-3p	SOX11
NEAT1	hsa-miR-141-3p	SOX11
TRAF3IP2-AS1	hsa-miR-141-3p	SOX11
XIST	hsa-miR-141-3p	SOX11
DLX6-AS1	hsa-miR-141-3p	SOX11
MALAT1	hsa-miR-141-3p	SOX11
DSCAM-AS1	hsa-miR-141-3p	SOX11
MYLK-AS1	hsa-miR-141-3p	SOX11
FGD5-AS1	hsa-miR-142-5p	SOX5
NEAT1	hsa-miR-142-5p	SOX5
COX10-AS1	hsa-miR-142-5p	SOX5
KCNQ1OT1	hsa-miR-142-5p	SOX5
LINC00473	hsa-miR-142-5p	SOX5
HCG18	hsa-miR-142-5p	SOX5
FGD5-AS1	hsa-miR-142-5p	SOX9
NEAT1	hsa-miR-142-5p	SOX9
COX10-AS1	hsa-miR-142-5p	SOX9
KCNQ1OT1	hsa-miR-142-5p	SOX9
LINC00473	hsa-miR-142-5p	SOX9
HCG18	hsa-miR-142-5p	SOX9
LIFR-AS1	hsa-miR-144-3p	SOX11
HCG11	hsa-miR-144-3p	SOX11
NEAT1	hsa-miR-144-3p	SOX11
MALAT1	hsa-miR-144-3p	SOX11
HCP5	hsa-miR-144-3p	SOX11
XIST	hsa-miR-144-3p	SOX11
GAS5	hsa-miR-144-3p	SOX11
DNAJC3-AS1	hsa-miR-144-3p	SOX11

LINC00476	hsa-miR-144-3p	SOX11
SNHG14	hsa-miR-144-3p	SOX11
JPX	hsa-miR-145-5p	SOX9
HCG18	hsa-miR-145-5p	SOX9
LINC00052	hsa-miR-145-5p	SOX9
SNHG1	hsa-miR-145-5p	SOX9
MALAT1	hsa-miR-145-5p	SOX9
PVT1	hsa-miR-145-5p	SOX9
KCNQ1OT1	hsa-miR-145-5p	SOX9
MEG3	hsa-miR-145-5p	SOX9
GRM5-AS1	hsa-miR-145-5p	SOX9
JPX	hsa-miR-145-5p	SOX10
HCG18	hsa-miR-145-5p	SOX10
LINC00052	hsa-miR-145-5p	SOX10
SNHG1	hsa-miR-145-5p	SOX10
MALAT1	hsa-miR-145-5p	SOX10
PVT1	hsa-miR-145-5p	SOX10
KCNQ1OT1	hsa-miR-145-5p	SOX10
MEG3	hsa-miR-145-5p	SOX10
GRM5-AS1	hsa-miR-145-5p	SOX10
JPX	hsa-miR-145-5p	SOX11
HCG18	hsa-miR-145-5p	SOX11
LINC00052	hsa-miR-145-5p	SOX11
SNHG1	hsa-miR-145-5p	SOX11
MALAT1	hsa-miR-145-5p	SOX11
PVT1	hsa-miR-145-5p	SOX11
KCNQ1OT1	hsa-miR-145-5p	SOX11
MEG3	hsa-miR-145-5p	SOX11
GRM5-AS1	hsa-miR-145-5p	SOX11
JPX	hsa-miR-145-5p	SOX2
HCG18	hsa-miR-145-5p	SOX2
LINC00052	hsa-miR-145-5p	SOX2
SNHG1	hsa-miR-145-5p	SOX2
MALAT1	hsa-miR-145-5p	SOX2
PVT1	hsa-miR-145-5p	SOX2
KCNQ1OT1	hsa-miR-145-5p	SOX2
MEG3	hsa-miR-145-5p	SOX2
GRM5-AS1	hsa-miR-145-5p	SOX2
LINC00115	hsa-miR-146b-5p	SOX4
XIST	hsa-miR-146b-5p	SOX4
HCG18	hsa-miR-146b-5p	SOX4
SNHG7	hsa-miR-146b-5p	SOX4
KCNQ1OT1	hsa-miR-146b-5p	SOX4
EPB41L4A-AS1	hsa-miR-146b-5p	SOX4
CRNDE	hsa-miR-146b-5p	SOX4
AC012615.1	hsa-miR-146b-5p	SOX4
MALAT1	hsa-miR-146b-5p	SOX4
NEAT1	hsa-miR-146b-5p	SOX4
NEAT1	hsa-miR-182-5p	SOX2
BOLA3-AS1	hsa-miR-182-5p	SOX2
PCGEM1	hsa-miR-182-5p	SOX2
KCNQ1OT1	hsa-miR-182-5p	SOX2
SNHG1	hsa-miR-182-5p	SOX2
SNHG10	hsa-miR-182-5p	SOX2
XIST	hsa-miR-182-5p	SOX2
NEAT1	hsa-miR-182-5p	SOX11
BOLA3-AS1	hsa-miR-182-5p	SOX11
PCGEM1	hsa-miR-182-5p	SOX11
KCNQ1OT1	hsa-miR-182-5p	SOX11
SNHG1	hsa-miR-182-5p	SOX11
SNHG10	hsa-miR-182-5p	SOX11
XIST	hsa-miR-182-5p	SOX11
NEAT1	hsa-miR-182-5p	SOX8
BOLA3-AS1	hsa-miR-182-5p	SOX8
PCGEM1	hsa-miR-182-5p	SOX8
KCNQ1OT1	hsa-miR-182-5p	SOX8
SNHG1	hsa-miR-182-5p	SOX8

SNHG10	hsa-miR-182-5p	SOX8
XIST	hsa-miR-182-5p	SOX8
NEAT1	hsa-miR-182-5p	SOX4
BOLA3-AS1	hsa-miR-182-5p	SOX4
PCGEM1	hsa-miR-182-5p	SOX4
KCNQ1OT1	hsa-miR-182-5p	SOX4
SNHG1	hsa-miR-182-5p	SOX4
SNHG10	hsa-miR-182-5p	SOX4
XIST	hsa-miR-182-5p	SOX4
MCM3AP-AS1	hsa-miR-187-3p	SOX4
KCNQ1OT1	hsa-miR-187-3p	SOX4
PVT1	hsa-miR-187-3p	SOX4
FTX	hsa-miR-192-5p	SOX4
KCNQ1OT1	hsa-miR-192-5p	SOX4
XIST	hsa-miR-192-5p	SOX4
FGD5-AS1	hsa-miR-195-5p	SOX5
PCBP1-AS1	hsa-miR-195-5p	SOX5
TRAF3IP2-AS1	hsa-miR-195-5p	SOX5
SNHG12	hsa-miR-195-5p	SOX5
HCG17	hsa-miR-195-5p	SOX5
ACTN1-AS1	hsa-miR-195-5p	SOX5
EPB41L4A-AS1	hsa-miR-195-5p	SOX5
HCG18	hsa-miR-195-5p	SOX5
NEAT1	hsa-miR-195-5p	SOX5
MCM3AP-AS1	hsa-miR-195-5p	SOX5
MEG3	hsa-miR-195-5p	SOX5
MEG8	hsa-miR-195-5p	SOX5
LINC00324	hsa-miR-195-5p	SOX5
SNHG1	hsa-miR-195-5p	SOX5
XIST	hsa-miR-195-5p	SOX5
LINC00473	hsa-miR-195-5p	SOX5
KCNQ1OT1	hsa-miR-195-5p	SOX5
DLX6-AS1	hsa-miR-195-5p	SOX5
PVT1	hsa-miR-195-5p	SOX5
MYLK-AS1	hsa-miR-200a-3p	SOX11
DSCAM-AS1	hsa-miR-200a-3p	SOX11
LINC00319	hsa-miR-200a-3p	SOX11
XIST	hsa-miR-200a-3p	SOX11
NEAT1	hsa-miR-200a-3p	SOX11
MALAT1	hsa-miR-200a-3p	SOX11
TRAF3IP2-AS1	hsa-miR-200a-3p	SOX11
KCNQ1OT1	hsa-miR-200a-3p	SOX11
DLX6-AS1	hsa-miR-200a-3p	SOX11
MALAT1	hsa-miR-200b-3p	SOX1
MCM3AP-AS1	hsa-miR-200b-3p	SOX1
XIST	hsa-miR-200b-3p	SOX1
KCNQ1OT1	hsa-miR-200b-3p	SOX1
NEAT1	hsa-miR-200b-3p	SOX1
HCG11	hsa-miR-204-5p	SOX4
LINC00472	hsa-miR-204-5p	SOX4
SNHG1	hsa-miR-204-5p	SOX4
NEAT1	hsa-miR-204-5p	SOX4
MALAT1	hsa-miR-204-5p	SOX4
KCNQ1OT1	hsa-miR-204-5p	SOX4
XIST	hsa-miR-204-5p	SOX4
MCM3AP-AS1	hsa-miR-204-5p	SOX4
DSCAM-AS1	hsa-miR-204-5p	SOX4
HCG11	hsa-miR-204-5p	SOX11
LINC00472	hsa-miR-204-5p	SOX11
SNHG1	hsa-miR-204-5p	SOX11
NEAT1	hsa-miR-204-5p	SOX11
MALAT1	hsa-miR-204-5p	SOX11
KCNQ1OT1	hsa-miR-204-5p	SOX11
XIST	hsa-miR-204-5p	SOX11
MCM3AP-AS1	hsa-miR-204-5p	SOX11
DSCAM-AS1	hsa-miR-204-5p	SOX11
LINC00174	hsa-miR-206	SOX9
DNMBP-AS1	hsa-miR-206	SOX9

LINC00242	hsa-miR-206	SOX9
SNHG14	hsa-miR-206	SOX9
HOTAIR	hsa-miR-206	SOX9
NEAT1	hsa-miR-206	SOX9
MALAT1	hsa-miR-206	SOX9
COX10-AS1	hsa-miR-206	SOX9
UCA1	hsa-miR-206	SOX9
MIAT	hsa-miR-206	SOX9
PVT1	hsa-miR-20a-5p	SOX11
EPB41L4A-AS1	hsa-miR-20a-5p	SOX11
HCG18	hsa-miR-20a-5p	SOX11
HCP5	hsa-miR-20a-5p	SOX11
THAP7-AS1	hsa-miR-20a-5p	SOX11
NEAT1	hsa-miR-20a-5p	SOX11
MALAT1	hsa-miR-20a-5p	SOX11
MAGI1-IT1	hsa-miR-20a-5p	SOX11
FGD5-AS1	hsa-miR-20a-5p	SOX11
XIST	hsa-miR-20a-5p	SOX11
TTTY15	hsa-miR-20a-5p	SOX11
KCNQ1OT1	hsa-miR-20a-5p	SOX11
HOTAIR	hsa-miR-20a-5p	SOX11
SNHG14	hsa-miR-20a-5p	SOX11
PVT1	hsa-miR-20a-5p	SOX4
EPB41L4A-AS1	hsa-miR-20a-5p	SOX4
HCG18	hsa-miR-20a-5p	SOX4
HCP5	hsa-miR-20a-5p	SOX4
THAP7-AS1	hsa-miR-20a-5p	SOX4
NEAT1	hsa-miR-20a-5p	SOX4
MALAT1	hsa-miR-20a-5p	SOX4
MAGI1-IT1	hsa-miR-20a-5p	SOX4
FGD5-AS1	hsa-miR-20a-5p	SOX4
XIST	hsa-miR-20a-5p	SOX4
TTTY15	hsa-miR-20a-5p	SOX4
KCNQ1OT1	hsa-miR-20a-5p	SOX4
HOTAIR	hsa-miR-20a-5p	SOX4
SNHG14	hsa-miR-20a-5p	SOX4
PVT1	hsa-miR-20a-5p	SOX9
EPB41L4A-AS1	hsa-miR-20a-5p	SOX9
HCG18	hsa-miR-20a-5p	SOX9
HCP5	hsa-miR-20a-5p	SOX9
THAP7-AS1	hsa-miR-20a-5p	SOX9
NEAT1	hsa-miR-20a-5p	SOX9
MALAT1	hsa-miR-20a-5p	SOX9
MAGI1-IT1	hsa-miR-20a-5p	SOX9
FGD5-AS1	hsa-miR-20a-5p	SOX9
XIST	hsa-miR-20a-5p	SOX9
TTTY15	hsa-miR-20a-5p	SOX9
KCNQ1OT1	hsa-miR-20a-5p	SOX9
HOTAIR	hsa-miR-20a-5p	SOX9
SNHG14	hsa-miR-20a-5p	SOX9
PVT1	hsa-miR-20a-5p	SOX5
EPB41L4A-AS1	hsa-miR-20a-5p	SOX5
HCG18	hsa-miR-20a-5p	SOX5
HCP5	hsa-miR-20a-5p	SOX5
THAP7-AS1	hsa-miR-20a-5p	SOX5
NEAT1	hsa-miR-20a-5p	SOX5
MALAT1	hsa-miR-20a-5p	SOX5
MAGI1-IT1	hsa-miR-20a-5p	SOX5
FGD5-AS1	hsa-miR-20a-5p	SOX5
XIST	hsa-miR-20a-5p	SOX5
TTTY15	hsa-miR-20a-5p	SOX5
KCNQ1OT1	hsa-miR-20a-5p	SOX5
HOTAIR	hsa-miR-20a-5p	SOX5
SNHG14	hsa-miR-20a-5p	SOX5
PVT1	hsa-miR-21-5p	SOX2
SNHG1	hsa-miR-21-5p	SOX2
MALAT1	hsa-miR-21-5p	SOX2

BRWD1-IT1	hsa-miR-21-5p	SOX2
XIST	hsa-miR-21-5p	SOX2
FTX	hsa-miR-21-5p	SOX2
FAM66E	hsa-miR-21-5p	SOX2
PVT1	hsa-miR-21-5p	SOX9
SNHG1	hsa-miR-21-5p	SOX9
MALAT1	hsa-miR-21-5p	SOX9
BRWD1-IT1	hsa-miR-21-5p	SOX9
XIST	hsa-miR-21-5p	SOX9
FTX	hsa-miR-21-5p	SOX9
FAM66E	hsa-miR-21-5p	SOX9
PVT1	hsa-miR-21-5p	SOX5
SNHG1	hsa-miR-21-5p	SOX5
MALAT1	hsa-miR-21-5p	SOX5
BRWD1-IT1	hsa-miR-21-5p	SOX5
XIST	hsa-miR-21-5p	SOX5
FTX	hsa-miR-21-5p	SOX5
FAM66E	hsa-miR-21-5p	SOX5
SCARNA9	hsa-miR-210-3p	SOX8
LINC00473	hsa-miR-210-3p	SOX8
XIST	hsa-miR-27b-3p	SOX11
ST7-AS1	hsa-miR-27b-3p	SOX11
NEAT1	hsa-miR-27b-3p	SOX11
GUSBP11	hsa-miR-27b-3p	SOX11
PVT1	hsa-miR-27b-3p	SOX11
DNAJC3-AS1	hsa-miR-27b-3p	SOX11
HCP5	hsa-miR-27b-3p	SOX11
KCNQ1OT1	hsa-miR-27b-3p	SOX11
KCNQ1OT1	hsa-miR-301b-3p	SOX4
XIST	hsa-miR-301b-3p	SOX4
BOLA3-AS1	hsa-miR-301b-3p	SOX4
FGD5-AS1	hsa-miR-301b-3p	SOX4
HCG18	hsa-miR-301b-3p	SOX4
HOTAIR	hsa-miR-301b-3p	SOX4
NEAT1	hsa-miR-301b-3p	SOX4
MCM3AP-AS1	hsa-miR-301b-3p	SOX4
MALAT1	hsa-miR-363-3p	SOX11
SNHG14	hsa-miR-363-3p	SOX11
XIST	hsa-miR-363-3p	SOX11
HNF1A-AS1	hsa-miR-363-3p	SOX11
MEG8	hsa-miR-363-3p	SOX11
JPX	hsa-miR-363-3p	SOX11
LINC00365	hsa-miR-363-3p	SOX11
KCNQ1OT1	hsa-miR-363-3p	SOX11
MALAT1	hsa-miR-363-3p	SOX4
SNHG14	hsa-miR-363-3p	SOX4
XIST	hsa-miR-363-3p	SOX4
HNF1A-AS1	hsa-miR-363-3p	SOX4
MEG8	hsa-miR-363-3p	SOX4
JPX	hsa-miR-363-3p	SOX4
LINC00365	hsa-miR-363-3p	SOX4
KCNQ1OT1	hsa-miR-363-3p	SOX4
PVT1	hsa-miR-365a-3p	SOX9
XIST	hsa-miR-365a-3p	SOX9
HCG18	hsa-miR-365a-3p	SOX9
GUSBP11	hsa-miR-365a-3p	SOX9
NEAT1	hsa-miR-365a-3p	SOX9
SNHG14	hsa-miR-365a-3p	SOX9
PVT1	hsa-miR-365b-3p	SOX9
NEAT1	hsa-miR-365b-3p	SOX9
XIST	hsa-miR-365b-3p	SOX9
HCG18	hsa-miR-365b-3p	SOX9
SNHG14	hsa-miR-365b-3p	SOX9
GUSBP11	hsa-miR-365b-3p	SOX9
RRN3P2	hsa-miR-429	SOX9
NEAT1	hsa-miR-429	SOX9
KCNQ1OT1	hsa-miR-429	SOX9
MCM3AP-AS1	hsa-miR-429	SOX9

LINC00174	hsa-miR-429	SOX9
LINC00365	hsa-miR-429	SOX9
MALAT1	hsa-miR-429	SOX9
XIST	hsa-miR-429	SOX9
RRN3P2	hsa-miR-429	SOX2
NEAT1	hsa-miR-429	SOX2
KCNQ1OT1	hsa-miR-429	SOX2
MCM3AP-AS1	hsa-miR-429	SOX2
LINC00174	hsa-miR-429	SOX2
LINC00365	hsa-miR-429	SOX2
MALAT1	hsa-miR-429	SOX2
XIST	hsa-miR-429	SOX2
HCG18	hsa-miR-497-5p	SOX11
LINC00324	hsa-miR-497-5p	SOX11
HCG17	hsa-miR-497-5p	SOX11
TRAF3IP2-AS1	hsa-miR-497-5p	SOX11
LINC00473	hsa-miR-497-5p	SOX11
MCM3AP-AS1	hsa-miR-497-5p	SOX11
XIST	hsa-miR-497-5p	SOX11
MEG3	hsa-miR-497-5p	SOX11
MEG8	hsa-miR-497-5p	SOX11
FGD5-AS1	hsa-miR-497-5p	SOX11
EPB41L4A-AS1	hsa-miR-497-5p	SOX11
PVT1	hsa-miR-497-5p	SOX11
KCNQ1OT1	hsa-miR-497-5p	SOX11
SNHG1	hsa-miR-497-5p	SOX11
DLX6-AS1	hsa-miR-497-5p	SOX11
ACTN1-AS1	hsa-miR-497-5p	SOX11
SNHG12	hsa-miR-497-5p	SOX11
PCBP1-AS1	hsa-miR-497-5p	SOX11
NEAT1	hsa-miR-497-5p	SOX11
MALAT1	hsa-miR-503-5p	SOX5
SNHG12	hsa-miR-503-5p	SOX5
NEAT1	hsa-miR-503-5p	SOX5
COX10-AS1	hsa-miR-503-5p	SOX5
LINC00460	hsa-miR-503-5p	SOX5
KCNQ1OT1	hsa-miR-93-5p	SOX4
NEAT1	hsa-miR-93-5p	SOX4
HCP5	hsa-miR-93-5p	SOX4
PVT1	hsa-miR-93-5p	SOX4
MALAT1	hsa-miR-93-5p	SOX4
HOTAIR	hsa-miR-93-5p	SOX4
EPB41L4A-AS1	hsa-miR-93-5p	SOX4
HCG18	hsa-miR-93-5p	SOX4
FGD5-AS1	hsa-miR-93-5p	SOX4
MAGI1-IT1	hsa-miR-93-5p	SOX4
TTTY15	hsa-miR-93-5p	SOX4
SNHG14	hsa-miR-93-5p	SOX4
THAP7-AS1	hsa-miR-93-5p	SOX4
XIST	hsa-miR-93-5p	SOX4
SLC25A5-AS1	hsa-miR-96-5p	SOX4
FGF14-IT1	hsa-miR-96-5p	SOX4
TP53TG1	hsa-miR-96-5p	SOX4
XIST	hsa-miR-96-5p	SOX4
UCA1	hsa-miR-96-5p	SOX4
MALAT1	hsa-miR-96-5p	SOX4
SLC25A5-AS1	hsa-miR-96-5p	SOX5
FGF14-IT1	hsa-miR-96-5p	SOX5
TP53TG1	hsa-miR-96-5p	SOX5
XIST	hsa-miR-96-5p	SOX5
UCA1	hsa-miR-96-5p	SOX5
MALAT1	hsa-miR-96-5p	SOX5

4.3. Identification of Key SOX Genes for Specificity and Diagnosis in GC

Five of 11 SOX genes in the ceRNA network were differentially expressed between normal (GTEx) and tumor (TCGA-STAD) tissues, including the down-regulated SOX2, and the other four up-regulated SOX genes, SOX4, SOX9, SOX11, and SOX14. However, we found SOX11 had no significantly expressed difference between tumor tissues and their paired normal tissues (Figure 4a). In addition, compared to different cancers, SOX9 was shown specifically in GC, and was highly expressed in the gastrointestinal tract (Figure S1). Then, ROC curve analysis was performed to compare the AUC value to evaluate the sensitivity and specificity of the above-mentioned SOX genes for the diagnosis of STAD in TCGA datasets. We found SOX9 and SOX4 had good sensitivities and specificities in GTEx and TCGA-STAD datasets. ROC curves of SOX9 and SOX4 were displayed (Figure 4b), showing high sensitivity and specificity with average AUC of 0.974 and 0.971 in GTEx and TCGA-STAD, 0.956 and 0.969 in TCGA-STAD, respectively. The results mean that SOX9 and SOX4 could effectively distinguish STAD patients from normal tissues. To investigate the prognostic impact of SOX genes, Kaplan-Meier survival curves and Log-rank tests were used to analyze the OS of STAD patients. As shown in (Figure 4c), high expression of SOX9 (HR = 0.65, Log-rank test $P = 0.015$) and SOX14 (HR = 0.58, Log-rank test $P = 0.008$) in tumors correlate with good prognosis, while high SOX4 (HR = 1.41, Log-rank test $P = 0.038$) correlates with bad prognosis. Taken together, these results suggested that SOX9 plays a key role in the tumorigenesis of gastric cancer. Thus, SOX9 was selected to further biological analysis.

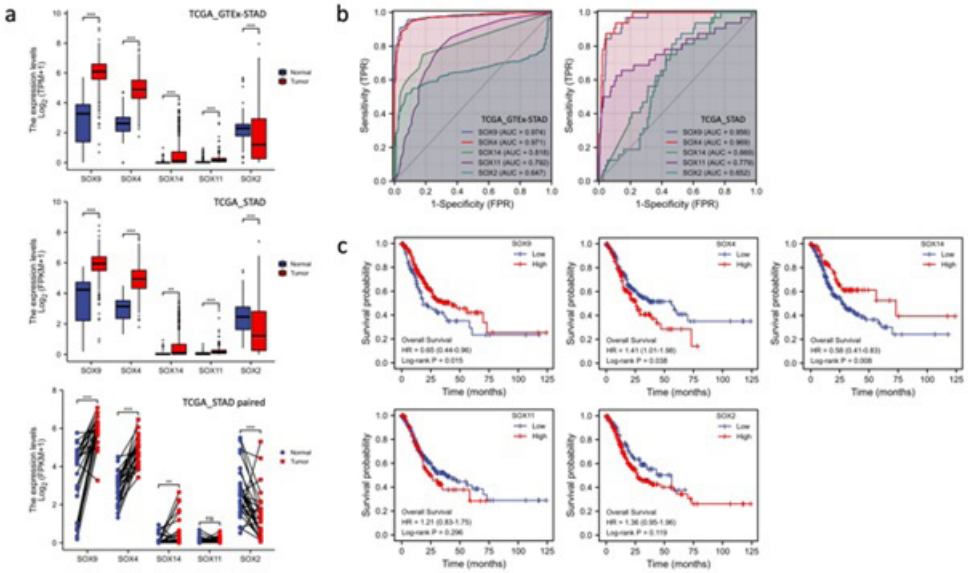

Figure 4: Differential expression and prognosis of SOX genes in ceRNA networks. (a) the expression of SOX genes between GC and normal tissues. (b) Receiver operating characterstic (ROC) curves were used to analyze the diagnostic value of SOX genes from the STAD, TCGA and GTEx database. (c) Kaplan-Meier analysis of SOX genes in GC patients for OS.

4.4. The Biological Processes of SOX9 Associated Degs

To explore the regulatory role of SOX9 on mRNA expression, the median value of its expression levels was applied as a cut-off to divide GC samples into high- and low-level groups. With the screening criteria adjust $P < 0.05$ and $|\log2FC| > 1.5$, 50 DEGs were identified which might be regulated by SOX9. Among them, 11 genes were significantly upregulated; while 39 genes were significantly downregulated, respectively (Table S6). To investigate the mechanisms associated with the SOX9 associated DEGs, GO enrichment analysis was carried out with the threshold set as adjusted $P < 0.05$. The significantly enriched GO terms were illustrated and available in (Figure 5a) and (Table S7). Most importantly, the up-regulated DEGs were mainly enriched in biological process terms including pattern specification process (GO:0007389), anterior/posterior pattern specification (GO:0009952), regionalization (GO:0003002), and proximal/distal pattern formation (GO:0009954) (Figure 5a, b). Meanwhile, the down-regulated DEGs were enriched in regulation of potassium ion transport (GO:0043266), sodium ion homeostasis (GO:0055078), cellular sodium ion homeostasis (GO:0006883), potassium ion transport (GO:0006813), positive regulation of amine transport (GO:0051954), etc. (Figure 5a, b). The top 10 DEGs which enriched in most GO terms were mainly including up-regulated DEGs, FEZF1, HOXC13, HOXC10, HOXC9, and HOXA11, and down-regulated DEGs, DPP6, ATP4B, CASQ2, KCNA1, ATP4A, and SFRP1 (Figure 5c).

Table S6: DEGs regulated by SOX9

	logFC	AveExpr	t	P.Value	adj.P.Val	B	Group
GAD1	1.640035393	0.664287786	7.12049115	4.94E-12	2.76E-10	16.74270366	up-regulated
HOXC9	1.593120148	0.456963888	6.767685121	4.60E-11	1.74E-09	14.62639097	up-regulated
FEZF1	1.899400227	-0.640277086	6.310884635	7.29E-10	1.76E-08	11.9830378	up-regulated
SP8	1.726151956	-2.713466643	6.076543895	2.84E-09	5.58E-08	10.69198694	up-regulated
DMBX1	1.572671224	-1.027120188	6.020715725	3.90E-09	7.24E-08	10.41045473	up-regulated
CST1	1.692103707	3.674401317	5.321141204	1.71E-07	1.83E-06	6.842039827	up-regulated
HOXC13	1.758331562	-1.905011829	5.092644222	5.42E-07	4.94E-06	5.858045923	up-regulated
HOXA11	1.553000253	0.078548383	4.99143275	8.92E-07	7.52E-06	5.414319791	up-regulated
HOXC10	1.690027846	1.457866186	4.693048824	3.69E-06	2.57E-05	4.082105143	up-regulated
ALPPL2	1.630237963	-0.164950967	4.483115909	9.59E-06	5.85E-05	3.233074874	up-regulated
HOXC12	1.554369365	-2.556457184	3.913738986	0.000106582	0.000467823	1.061455607	up-regulated
SERTM1	-1.706517054	-4.849200403	-7.851738567	3.71E-14	4.57E-12	21.27766187	down-regulated
MAL	-2.158083826	0.530293461	-7.685456147	1.16E-13	1.20E-11	20.25521349	down-regulated
CPB1	-1.787350383	-2.937025906	-7.565048522	2.63E-13	2.35E-11	19.30224704	down-regulated
ADCYAP1R1	-1.584179335	-1.479614968	-7.290236985	1.64E-12	1.07E-10	17.57174516	down-regulated
NRXN1	-1.626430024	-0.609552904	-7.095984338	5.78E-12	3.12E-10	16.46173476	down-regulated
FCER1A	-1.549331811	-0.685205343	-7.053918077	7.57E-12	3.98E-10	16.20281664	down-regulated
PCSK2	-1.770639555	-1.896651882	-6.959654179	1.38E-11	6.46E-10	15.59846496	down-regulated
SFRP1	-1.78776792	2.607586976	-6.793574183	3.92E-11	1.54E-09	14.89506004	down-regulated
CCL21	-1.571594363	4.063740386	-6.774335468	4.42E-11	1.70E-09	14.73799787	down-regulated
CADM3	-1.791336432	0.133796487	-6.720673811	6.16E-11	2.23E-09	14.32470461	down-regulated
SORCS1	-1.507072323	-0.968038477	-6.577204382	1.48E-10	4.65E-09	13.42019438	down-regulated
DPT	-1.501595193	2.175561855	-6.513981722	2.17E-10	6.41E-09	13.25381313	down-regulated
SCN7A	-1.646228275	0.298181401	-6.425670251	3.69E-10	9.91E-09	12.66252423	down-regulated
CASQ2	-1.619729182	0.594689102	-6.406100001	4.15E-10	1.09E-08	12.5729322	down-regulated
SYT4	-1.709783425	-3.330940184	-6.401730127	4.26E-10	1.11E-08	12.46205571	down-regulated
PLP1	-1.728831192	-0.73688783	-6.150350406	1.86E-09	3.87E-08	11.09536923	dow n-regulated
HSPB6	-1.580328253	4.988708022	-6.105056869	2.41E-09	4.85E-08	10.81016777	down-regulated
ADH7	-2.149126011	-3.549468967	-6.093775929	2.57E-09	5.12E-08	10.80381014	down-regulated
AQP4	-1.657810656	-3.619232511	-6.04207467	3.45E-09	6.54E-08	10.53307264	down-regulated
CARTPT	-1.96913633	-3.08828195	-6.014053092	4.05E-09	7.49E-08	10.36891122	down-regulated
PPP1R1A	-1.54491395	0.118278096	-5.927027038	6.60E-09	1.14E-07	9.961163785	down-regulated
C2orf40	-1.828854948	0.769922292	-5.91696041	6.99E-09	1.20E-07	9.935722152	down-regulated
DPP6	-1.530007475	-1.026259851	-5.909250052	7.30E-09	1.24E-07	9.816003129	down-regulated
CWH43	-1.844970215	-4.068682113	-5.901238442	7.63E-09	1.29E-07	9.810421071	down-regulated
MYOC	-2.13070366	-1.436373822	-5.838083116	1.08E-08	1.73E-07	9.451151583	down-regulated
C7	-1.690366384	3.817593116	-5.787747069	1.43E-08	2.18E-07	9.188475204	down-regulated
KCNA1	-1.686890998	-3.091895063	-5.75012865	1.76E-08	2.59E-07	9.012334079	down-regulated
PDZRN4	-1.518335415	-0.161335707	-5.726419914	2.00E-08	2.89E-07	8.919413116	down-regulated
ADH1B	-1.662126347	2.770725182	-5.488704754	7.15E-08	8.65E-07	7.727990177	down-regulated
ASB5	-1.798335316	-2.147687642	-5.103110296	5.15E-07	4.73E-06	5.89951586	down-regulated
VIP	-1.532071912	-1.038673441	-5.027025009	7.49E-07	6.47E-06	5.559317296	down-regulated
TCEAL2	-1.500425907	-0.638774908	-4.860579563	1.68E-06	1.30E-05	4.827303638	down-regulated
SST	-1.759818838	-1.09833944	-4.535716907	7.57E-06	4.79E-05	3.450185434	down-regulated
ATP4A	-1.724719655	-1.672065157	-4.419569696	1.27E-05	7.46E-05	2.979841615	down-regulated
PGA5	-1.754080793	-2.72801862	-4.106082443	4.87E-05	0.000238674	1.766178343	down-regulated
ATP4B	-1.548749478	-2.129601874	-3.811140614	0.000159814	0.000661566	0.702382269	down-regulated
PGA3	-1.85831835	-1.492164277	-3.487943375	0.000540089	0.001911362	-0.383922192	down-regulated
GKN2	-1.712348359	0.326131328	-3.307413366	0.001025689	0.003295314	-1.003574685	down-regulated
GKN1	-1.763047998	1.231916503	-3.056981124	0.002383943	0.006859769	-1.813528594	down-regulated

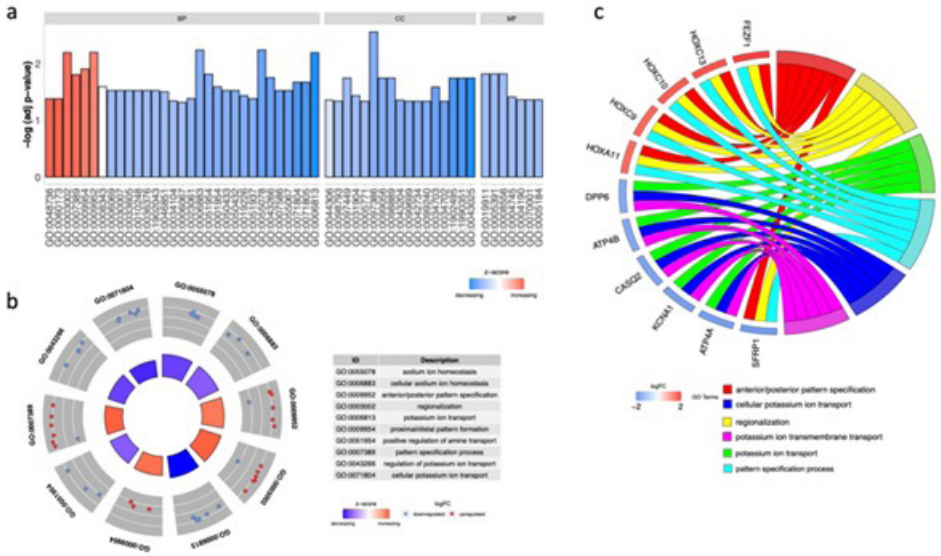

Figure 5: Enrichment analysis of the DEGs regulated by SOX9. (a) illustrate the elements significantly enriched in the three GO categories; (b) the top 10 elements significantly enriched in the GO categories; (c) the significant GO terms associated with DEGs with a p-value of less than 0.05.

Table S7: GO analysis of the genes differentially expressed associated with SOX9

Category	ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	geneID	Count
BP	GO:0055078	sodium ion homeostasis	4/46	52/18670	8.01E-06	0.005778974	0.004635698	SCN7A/C7/ATP4A/ATP4B	4
BP	GO:0006883	cellular sodium ion homeostasis	3/46	17/18670	9.29E-06	0.005778974	0.004635698	C7/ATP4A/ATP4B	3
BP	GO:0009952	anterior/ posterior pattern specification	6/46	219/18670	1.54E-05	0.00638592	0.005122569	HOXC9/FEZF1/HOXC13 /HOXA11/HOXC10/SFRP1	6
BP	GO:0003002	regionalization	7/46	351/18670	2.23E-05	0.006424355	0.0051534	HOXC9/FEZF1/SP8 /HOXC13/HOXA11 /HOXC10/SFRP1	7
BP	GO:0006813	potassium ion transport	6/46	240/18670	2.58E-05	0.006424355	0.0051534	CASQ2/DPP6/KCNA1 /VIP/ATP4A/ATP4B	6
BP	GO:0009954	proximal/ distal pattern formation	3/46	31/18670	5.99E-05	0.012429472	0.009970502	SP8/HOXA11/HOXC10	3
BP	GO:0051954	positive regulation of amine transport	3/46	35/18670	8.67E-05	0.015405951	0.012358133	SYT4/CARTPT/VIP	3
BP	GO:0007389	pattern specification process	7/46	446/18670	0.000101304	0.015752711	0.012636292	HOXC9/FEZF1/SP8 /HOXC13/HOXA11 /HOXC10/SFRP1	7
BP	GO:0043266	regulation of potassium ion transport	4/46	105/18670	0.000128529	0.017765523	0.014250902	CASQ2/DPP6/KCNA1/VIP	4
BP	GO:0071804	cellular potassium ion transport	5/46	217/18670	0.000188398	0.02130607	0.017091009	CASQ2/DPP6/KCNA1 /ATP4A/ATP4B	5
BP	GO:0071805	potassium ion transmembrane transport	5/46	217/18670	0.000188398	0.02130607	0.017091009	CASQ2/DPP6/KCNA1 /ATP4A/ATP4B	5
BP	GO:0008343	adult feeding behavior	2/46	10/18670	0.000263911	0.025676648	0.020596939	DMBX1/CARTPT	2
BP	GO:0001954	positive regulation of cell-matrix adhesion	3/46	51/18670	0.000268325	0.025676648	0.020596939	SFRP1/CCL21/MYOC	3

BP	GO:0007586	digestion	4/46	139/18670	0.000376698	0.029988568	0.024055816	SST/PGA5/PGA3/GKN1	4
BP	GO:0006069	ethanol oxidation	2/46	12/18670	0.000385855	0.029988568	0.024055816	ADH7/ADH1B	2
BP	GO:0030007	cellular potassium ion homeostasis	2/46	13/18670	0.000455295	0.029988568	0.024055816	ATP4A/ATP4B	2
BP	GO:0033605	positive regulation of catecholamine secretion	2/46	13/18670	0.000455295	0.029988568	0.024055816	CARTPT/VIP	2
BP	GO:0050433	regulation of catecholamine secretion	3/46	62/18670	0.000478156	0.029988568	0.024055816	SYT4/CARTPT/VIP	3
BP	GO:0050432	catecholamine secretion	3/46	64/18670	0.000524945	0.029988568	0.024055816	SYT4/CARTPT/VIP	3
BP	GO:0010248	establishment or maintenance of transmembrane electrochemical gradient	2/46	14/18670	0.000530344	0.029988568	0.024055816	ATP4A/ATP4B	2
BP	GO:0036376	sodium ion export across plasma membrane	2/46	14/18670	0.000530344	0.029988568	0.024055816	ATP4A/ATP4B	2
BP	GO:1902043	positive regulation of extrinsic apoptotic signaling pathway via death domain receptors	2/46	14/18670	0.000530344	0.029988568	0.024055816	MAL/SFRP1	2
BP	GO:0055067	monovalent inorganic cation homeostasis	4/46	154/18670	0.00055487	0.030011244	0.024074005	SCN7A/C7/ATP4A/ATP4B	4
BP	GO:0046851	negative regulation of bone remodeling	2/46	15/18670	0.000610976	0.031668932	0.025403746	SFRP1/CARTPT	2
BP	GO:0019226	transmission of nerve impulse	3/46	72/18670	0.00074116	0.036880121	0.029583986	SCN7A/CARTPT/KCNA1	3
BP	GO:0023061	signal release	6/46	462/18670	0.000899868	0.041525079	0.033310014	GAD1/NRXN1/SFRP1/SYT4/CARTPT/VIP	6
BP	GO:0051937	catecholamine transport	3/46	77/18670	0.000901268	0.041525079	0.033310014	SYT4/CARTPT/VIP	3
BP	GO:0048736	appendage development	4/46	179/18670	0.000973787	0.041772111	0.033508175	SP8/HOXC13/HOXA11/HOXC10	4
BP	GO:0060173	limb development	4/46	179/18670	0.000973787	0.041772111	0.033508175	SP8/HOXC13/HOXA11/HOXC10	4
BP	GO:0034104	negative regulation of tissue remodeling	2/46	20/18670	0.001096938	0.045486342	0.036487606	SFRP1/CARTPT	2
BP	GO:0006067	ethanol metabolic process	2/46	21/18670	0.001210505	0.048576392	0.038966339	ADH7/ADH1B	2
CC	GO:0097386	glial cell projection	3/47	24/19717	2.48E-05	0.002778253	0.001958355	SCN7A/SYT4/AQP4	3
CC	GO:0097449	astrocyte projection	2/47	12/19717	0.000361519	0.018052487	0.012724968	SYT4/AQP4	2
CC	GO:0099056	integral component of presynaptic membrane	3/47	73/19717	0.000702377	0.018052487	0.012724968	NRXN1/CADM3/KCNA1	3

CC	GO:0098889	intrinsic component of presynaptic membrane	3/47	82/19717	0.00098522	0.018052487	0.012724968	NRXN1/CADM3/KCNA1	3
CC	GO:1902495	transmembrane transporter complex	5/47	324/19717	0.001012224	0.018052487	0.012724968	SCN7A/CASQ2/DPP6/KCNA1/ATP4B	5
CC	GO:0043025	neuronal cell body	6/47	497/19717	0.001112403	0.018052487	0.012724968	NRXN1/PCSK2/SYT4/KCNA1/VIP/SST	6
CC	GO:1990351	transporter complex	5/47	332/19717	0.00112828	0.018052487	0.012724968	SCN7A/CASQ2/DPP6/KCNA1/ATP4B	5
CC	GO:0034703	cation channel complex	4/47	220/19717	0.00184761	0.02586654	0.018232993	SCN7A/CASQ2/DPP6/KCNA1	4
CC	GO:0031904	endosome lumen	2/47	34/19717	0.002971979	0.036984621	0.026069987	PGA5/PGA3	2
CC	GO:0043204	perikaryon	3/47	134/19717	0.004000686	0.044226924	0.031174993	PCSK2/KCNA1/VIP	3
CC	GO:0044306	neuron projection terminus	3/47	138/19717	0.004343716	0.044226924	0.031174993	GAD1/SYT4/KCNA1	3
CC	GO:0034702	ion channel complex	4/47	301/19717	0.005669263	0.046167101	0.0325426	SCN7A/CASQ2/DPP6/KCNA1	4
CC	GO:0099699	integral component of synaptic membrane	3/47	152/19717	0.005682734	0.046167101	0.0325426	NRXN1/CADM3/KCNA1	3
CC	GO:0098793	presynapse	5/47	491/19717	0.006086082	0.046167101	0.0325426	GAD1/NRXN1/CADM3/SYT4/KCNA1	5
CC	GO:0005771	multivesicular body	2/47	51/19717	0.00658293	0.046167101	0.0325426	PGA5/PGA3	2
CC	GO:0042734	presynaptic membrane	3/47	161/19717	0.006660646	0.046167101	0.0325426	NRXN1/CADM3/KCNA1	3
CC	GO:0099240	intrinsic component of synaptic membrane	3/47	164/19717	0.007007506	0.046167101	0.0325426	NRXN1/CADM3/KCNA1	3
MF	GO:0019911	structural constituent of myelin sheath	2/43	10/17697	0.000256323	0.015222942	0.011524217	MAL/PLP1	2
MF	GO:0005391	sodium: potassium\ exchanging ATPase activity	2/43	11/17697	0.0003128	0.015222942	0.011524217	ATP4A/ATP4B	2
MF	GO:0008556	potassium-transporting ATPase activity	2/43	11/17697	0.0003128	0.015222942	0.011524217	ATP4A/ATP4B	2
MF	GO:0004745	retinol dehydrogenase activity	2/43	20/17697	0.001065682	0.038897382	0.029446468	ADH7/ADH1B	2
MF	GO:0004190	aspartic-type endopeptidase activity	2/43	25/17697	0.001669739	0.043678441	0.033065871	PGA5/PGA3	2
MF	GO:0070001	aspartic-type peptidase activity	2/43	26/17697	0.001806099	0.043678441	0.033065871	PGA5/PGA3	2
MF	GO:0005184	neuropeptide hormone activity	2/43	28/17697	0.002094172	0.043678441	0.033065871	CARTPT/VIP	2

Table S8: Co-expressed gene with SOX9

gene	correlation	pvalue
ZNF252P-AS1	0.453575674	4.79E-22
ZDHHC20-IT1	0.403476172	2.29E-17
Z98884.2	0.47494775	2.73E-24
Z94721.2	0.42315783	4.12E-19
Z94721.1	0.481702504	4.93E-25
Z83851.2	0.560370752	5.02E-35
Z83851.1	0.60094179	2.59E-41
Z82243.1	0.411320721	4.77E-18
WASHC5-AS1	0.435320211	3.00E-20
VPS9D1-AS1	0.530321806	6.74E-31
UBL7-AS1	0.424651384	3.00E-19
UBE2Q1-AS1	0.472508201	5.01E-24
U62317.3	0.477014879	1.62E-24
U47924.1	0.457441484	1.93E-22
TUG1	0.426922629	1.85E-19
TRIM31-AS1	0.599043854	5.34E-41
TONSL-AS1	0.414113383	2.70E-18
TNRC6C-AS1	0.457906722	1.73E-22
TNFRSF14-AS1	0.477354183	1.49E-24
TNFRSF10A-AS1	0.506635807	6.36E-28
TMPO-AS1	0.537333031	7.99E-32
TIPARP-AS1	0.41190017	4.24E-18
THAP9-AS1	0.461190396	7.92E-23
TFAP2A-AS1	0.417594228	1.32E-18
STAG3L5P-PVRIG2P-PILRB	0.402758149	2.64E-17
SPINT1-AS1	0.609883044	8.01E-43
SPAG5-AS1	0.419532992	8.81E-19
SOX9-AS1	0.497067959	8.72E-27
SNHG4	0.48966233	6.25E-26
SNHG3	0.420531437	7.15E-19
SNHG20	0.471911339	5.82E-24
SNHG17	0.503612147	1.47E-27
SNHG16	0.439814535	1.11E-20
SNHG15	0.511691565	1.54E-28
SNHG12	0.416073404	1.80E-18
SNHG11	0.500452056	3.49E-27
SNHG1	0.45788203	1.74E-22
SMG7-AS1	0.420436915	7.29E-19
SLX1A-SULT1A3	0.425070107	2.75E-19
SLCO4A1-AS1	0.486052568	1.61E-25
SLC7A11-AS1	0.401707867	3.25E-17
SLC25A25-AS1	0.553401371	4.96E-34
SLC12A9-AS1	0.488581602	8.30E-26
SEPT4-AS1	0.445105579	3.37E-21
SCARNA15	0.414582899	2.45E-18
SAMD12-AS1	0.585369146	8.54E-39
RUSC1-AS1	0.455588346	2.99E-22
RPARP-AS1	0.469648664	1.02E-23
RHPN1-AS1	0.426793129	1.90E-19
RASAL2-AS1	0.504221259	1.24E-27
RALY-AS1	0.474090266	3.38E-24
PVT1	0.437288675	1.94E-20
PTOV1-AS2	0.417115579	1.45E-18
PTGES2-AS1	0.445110028	3.37E-21
PRR7-AS1	0.413994186	2.77E-18
PPP1R26-AS1	0.48243829	4.08E-25
POC1B-AS1	0.408140063	9.06E-18
PLUT	0.421370825	5.99E-19
PKP4-AS1	0.431672473	6.65E-20
PITRM1-AS1	0.429980085	9.59E-20
PINK1-AS	0.405503819	1.53E-17
PGM5-AS1	-0.482725258	3.79E-25
PDXDC2P-NPIPB14P	0.439086308	1.30E-20
PCAT7	0.581619349	3.29E-38
PCAT1	0.404299658	1.95E-17
OGFRP1	0.562611597	2.38E-35

NRAV	0.423212438	4.07E-19
NORAD	0.428096248	1.44E-19
NDUFB2-AS1	0.418891201	1.01E-18
NCK1-AS1	0.403456396	2.30E-17
MNX1-AS2	0.566518405	6.36E-36
MNX1-AS1	0.604187202	7.43E-42
MIR4435-2HG	0.538523534	5.53E-32
MIR200CHG	0.528093715	1.31E-30
MIR194-2HG	0.529390973	8.92E-31
MEF2C-AS1	-0.422598522	4.63E-19
MCM3AP-AS1	0.434200373	3.83E-20
MAPKAPK5-AS1	0.425804052	2.35E-19
MAL2	0.589736156	1.73E-39
MAFG-AS1	0.508609784	3.67E-28
LINC02557	-0.42580475	2.35E-19
LINC02500	-0.442147376	6.57E-21
LINC02363	0.407082113	1.12E-17
LINC02313	0.471773731	6.02E-24
LINC02166	0.417145247	1.45E-18
LINC02097	0.456981566	2.16E-22
LINC02041	0.437240244	1.96E-20
LINC02038	0.484829113	2.21E-25
LINC02014	0.527034417	1.80E-30
LINC01979	0.607377042	2.15E-42
LINC01978	0.523586916	4.99E-30
LINC01909	0.414889528	2.30E-18
LINC01843	0.505850695	7.91E-28
LINC01836	0.467708452	1.64E-23
LINC01814	0.579167119	7.89E-38
LINC01572	0.480285968	7.08E-25
LINC01497	-0.421411833	5.94E-19
LINC01342	0.56412642	1.43E-35
LINC01311	0.409907134	6.35E-18
LINC01232	0.553752809	4.43E-34
LINC01176	0.429834751	9.90E-20
LINC01132	0.456603843	2.36E-22
LINC01123	0.572826772	7.29E-37
LINC01106	0.55241902	6.82E-34
LINC00880	0.420064657	7.88E-19
LINC00853	0.465913709	2.54E-23
LINC00844	-0.40741337	1.05E-17
LINC00659	0.489655464	6.27E-26
LINC00628	0.529591331	8.40E-31
LINC00624	0.416873761	1.53E-18
LINC00543	0.471778616	6.01E-24
LINC00514	0.409688519	6.63E-18
LINC00511	0.666007609	1.66E-53
LINC00467	0.445186669	3.31E-21
LINC00449	0.418123635	1.18E-18
LINC00299	0.400195722	4.37E-17
LINC00239	0.420955677	6.54E-19
LBX2-AS1	0.585300044	8.75E-39
LACTB2-AS1	0.402483732	2.79E-17
KDM4A-AS1	0.446642999	2.37E-21
IQCH-AS1	0.444595227	3.78E-21
HOXC-AS2	0.519041488	1.88E-29
HOXC-AS1	0.458424133	1.53E-22
HOXA11-AS	0.405312315	1.59E-17
HOTAIR	0.443525079	4.82E-21
HNF4A-AS1	0.424381014	3.18E-19
HNF1A-AS1	0.521627665	8.87E-30
HCG18	0.422316911	4.91E-19
GRTP1-AS1	0.417168934	1.44E-18
GPRC5D-AS1	0.520756483	1.14E-29
FP700125.1	0.401769129	3.21E-17
FOXP4-AS1	0.515634329	5.02E-29
FOXD2-AS1	0.619639826	1.59E-44
FEZF1-AS1	0.487661892	1.06E-25

FBXL19-AS1	0.419833158	8.27E-19
ELF3-AS1	0.596515201	1.39E-40
EHMT2-AS1	0.412118244	4.05E-18
EBLN3P	0.41672716	1.58E-18
DTX2P1-UPK3BP1-PMS2P11	0.445546266	3.05E-21
DSG2-AS1	0.479368218	8.95E-25
DNMBP-AS1	0.55346477	4.86E-34
DLGAP1-AS2	0.43385243	4.14E-20
DLEU7-AS1	0.48598814	1.63E-25
DLEU2	0.4417194	7.24E-21
DLEU1	0.478362558	1.15E-24
DKFZP434K028	0.511422746	1.66E-28
DGUOK-AS1	0.401622165	3.30E-17
DDX11-AS1	0.455047753	3.40E-22
DCST1-AS1	0.4965304	1.01E-26
CYP4A22-AS1	0.490100489	5.57E-26
CIRBP-AS1	0.40412157	2.02E-17
CHL1-AS2	-0.438812165	1.39E-20
CASC8	0.426509723	2.02E-19
CAPN10-AS1	0.491466939	3.89E-26
C9orf163	0.516966667	3.42E-29
C6orf99	0.461082343	8.13E-23
C2orf48	0.524999769	3.29E-30
C1orf147	0.482850317	3.67E-25
C10orf91	0.44612024	2.68E-21
C10orf111	0.424437089	3.14E-19
BX890604.1	0.481293803	5.48E-25
BX470102.1	0.495499175	1.33E-26
BX255925.1	0.425190344	2.68E-19
BLACAT1	0.588834384	2.41E-39
BBOX1-AS1	0.409808488	6.47E-18
ATP2C2-AS1	0.413020191	3.37E-18
ASH1L-AS1	0.419228176	9.38E-19
ARMCX3-AS1	-0.426443365	2.05E-19
ARHGEF38-IT1	0.488854623	7.73E-26
APTR	0.412101543	4.07E-18
AP006621.4	0.508172318	4.14E-28
AP006284.1	0.508853926	3.42E-28
AP005233.2	0.409864719	6.40E-18
AP005136.2	0.518060183	2.50E-29
AP003555.2	0.409094444	7.48E-18
AP002449.1	0.424611532	3.03E-19
AP001453.3	0.43079996	8.03E-20
AP001453.2	0.448549326	1.53E-21
AP001372.2	0.442067812	6.69E-21
AP001258.1	0.430446621	8.67E-20
AP001107.9	0.478669785	1.07E-24
AP001107.6	0.417002088	1.49E-18
AP001107.5	-0.43272199	5.29E-20
AP000845.1	0.428016217	1.46E-19
AP000802.1	-0.402481716	2.79E-17
AP000697.1	0.499538881	4.47E-27
AP000442.2	0.444663156	3.72E-21
ANKRD10-IT1	0.409972928	6.26E-18
AL928654.3	0.447215903	2.08E-21
AL731571.1	0.434208222	3.83E-20
AL731566.1	0.406166159	1.34E-17
AL691482.3	0.663929622	4.53E-53
AL671710.1	0.478430012	1.14E-24
AL662797.3	0.429275073	1.12E-19
AL606489.1	0.587042637	4.65E-39
AL592103.1	0.41430037	2.60E-18
AL591895.1	0.463620527	4.42E-23
AL590729.1	0.406080147	1.37E-17
AL590666.2	0.516883492	3.51E-29
AL590652.1	0.443002282	5.42E-21
AL590133.1	0.413212362	3.24E-18
AL583810.1	0.486997058	1.26E-25

AL512413.1	0.504809522	1.05E-27
AL451050.2	0.503062986	1.71E-27
AL451042.2	0.415880071	1.88E-18
AL451042.1	0.44073159	9.03E-21
AL445524.1	0.409626779	6.72E-18
AL445231.1	0.53755577	7.46E-32
AL391988.1	0.404169422	2.00E-17
AL391845.2	0.451294729	8.15E-22
AL391832.2	0.438799479	1.39E-20
AL391244.3	0.43148594	6.92E-20
AL391244.1	0.469434914	1.07E-23
AL391095.1	0.400241109	4.33E-17
AL391069.2	0.435240953	3.05E-20
AL390728.6	0.410931718	5.16E-18
AL390719.2	0.658950469	4.89E-52
AL365436.2	0.44006369	1.05E-20
AL365181.3	0.521144867	1.02E-29
AL365181.2	0.417250618	1.41E-18
AL359075.2	0.414254309	2.62E-18
AL358115.1	0.492646971	2.84E-26
AL356299.2	0.502027112	2.27E-27
AL355802.3	0.44807513	1.71E-21
AL355802.1	0.440876458	8.74E-21
AL355488.2	0.412015634	4.14E-18
AL355353.1	0.404314559	1.94E-17
AL163051.1	0.416460661	1.67E-18
AL162727.2	0.450260362	1.04E-21
AL162595.1	0.53303446	2.97E-31
AL161891.1	0.468499276	1.35E-23
AL158166.2	0.45262648	5.98E-22
AL158166.1	0.511329942	1.71E-28
AL157838.1	0.496167842	1.11E-26
AL139289.2	0.414573404	2.46E-18
AL139289.1	0.403402212	2.33E-17
AL139246.5	0.487197326	1.19E-25
AL139035.1	0.434629296	3.49E-20
AL138756.1	0.574273095	4.41E-37
AL137782.1	0.474829492	2.81E-24
AL137060.1	0.429991299	9.57E-20
AL136221.1	0.474804192	2.83E-24
AL135999.1	0.43541679	2.93E-20
AL133410.1	0.457266481	2.01E-22
AL133406.2	0.442543778	6.01E-21
AL133215.2	0.552314475	7.06E-34
AL133215.1	0.493656275	2.17E-26
AL132712.2	0.428678129	1.27E-19
AL132712.1	0.530245196	6.90E-31
AL132639.3	0.449810888	1.15E-21
AL121992.3	0.413401968	3.12E-18
AL121944.1	0.481888057	4.70E-25
AL121895.1	0.416315314	1.72E-18
AL121839.2	0.500279331	3.65E-27
AL121832.3	0.527436087	1.60E-30
AL121832.1	0.421274407	6.12E-19
AL121782.1	0.404965757	1.71E-17
AL121772.1	0.432106219	6.05E-20
AL118506.1	0.419489667	8.88E-19
AL118505.1	0.595389638	2.12E-40
AL117382.2	0.438238545	1.57E-20
AL117382.1	0.481210737	5.59E-25
AL109615.3	0.503519126	1.51E-27
AL109613.1	0.512407936	1.26E-28
AL096828.3	0.457068578	2.11E-22
AL080317.1	0.405618844	1.50E-17
AL078644.1	0.536218128	1.13E-31
AL078587.1	0.436107601	2.52E-20
AL078459.1	0.410748313	5.35E-18

AL049555.1	0.598977077	5.48E-41
AL035661.1	0.503223547	1.63E-27
AL035252.3	0.511315504	1.71E-28
AL034550.1	0.535320812	1.48E-31
AL034549.2	0.519569279	1.61E-29
AL034549.1	0.503474182	1.52E-27
AL033527.3	0.405951846	1.40E-17
AL031775.1	0.409253053	7.24E-18
AL031123.2	0.545570566	6.11E-33
AL024508.2	0.618699783	2.33E-44
AL023284.4	0.58897545	2.29E-39
AL022322.1	0.562821809	2.21E-35
AL021578.1	0.426219381	2.15E-19
AL021453.1	0.453738101	4.62E-22
ACBD3-AS1	0.437292858	1.94E-20
AC245140.2	0.461141417	8.02E-23
AC234772.2	0.513111707	1.03E-28
AC233992.3	0.421387272	5.97E-19
AC145207.5	0.420810654	6.74E-19
AC138393.3	0.404477017	1.88E-17
AC137932.3	0.410933786	5.16E-18
AC133065.4	0.420872117	6.66E-19
AC132872.3	0.410868937	5.23E-18
AC131009.3	0.463455909	4.60E-23
AC130456.4	0.506197489	7.18E-28
AC130456.3	0.579180659	7.85E-38
AC129507.3	0.495072282	1.49E-26
AC129507.2	0.416737474	1.57E-18
AC128688.2	0.543866905	1.05E-32
AC125494.1	0.409440828	6.97E-18
AC125257.1	0.452073748	6.80E-22
AC124798.1	0.453918033	4.43E-22
AC124283.2	0.467754555	1.62E-23
AC121338.2	0.478617972	1.08E-24
AC120114.2	0.505209014	9.44E-28
AC117498.2	0.512096744	1.37E-28
AC116552.1	0.442194774	6.50E-21
AC116025.2	0.420729995	6.86E-19
AC114488.1	0.479811818	7.99E-25
AC112220.4	0.493233822	2.43E-26
AC112220.2	0.43998833	1.07E-20
AC109460.2	0.456613397	2.35E-22
AC109322.1	0.46108785	8.12E-23
AC108860.2	0.686789661	4.43E-58
AC108751.4	0.426141323	2.19E-19
AC108673.2	0.4251816	2.68E-19
AC108463.2	0.404561373	1.85E-17
AC108134.1	0.569446954	2.34E-36
AC106886.2	0.515418599	5.34E-29
AC106876.1	0.421913095	5.35E-19
AC106789.1	-0.460296718	9.81E-23
AC106782.6	0.429317279	1.11E-19
AC106782.2	0.441091819	8.33E-21
AC106772.1	0.411089787	5.00E-18
AC105935.2	0.403970564	2.08E-17
AC105935.1	0.427671533	1.58E-19
AC105429.1	0.407797869	9.70E-18
AC105389.3	-0.405477269	1.54E-17
AC105219.4	0.57585072	2.54E-37
AC105219.2	0.44357217	4.77E-21
AC105137.3	0.422108662	5.13E-19
AC104472.1	0.427247025	1.73E-19
AC103760.1	0.448862901	1.43E-21
AC103563.7	-0.466915526	1.99E-23
AC100861.1	0.629839076	2.27E-46
AC099850.3	0.637501634	8.38E-48
AC099676.1	0.611035984	5.08E-43
AC099568.2	0.497008439	8.86E-27

AC099518.4	0.498326563	6.21E-27
AC099518.2	0.47678284	1.72E-24
AC098869.2	0.502203552	2.16E-27
AC097639.1	0.588308562	2.93E-39
AC096536.3	0.432162233	5.98E-20
AC096536.1	0.438755255	1.40E-20
AC093484.5	0.496665135	9.72E-27
AC093157.2	0.479675677	8.27E-25
AC092910.3	0.419828911	8.28E-19
AC092755.2	0.405757455	1.46E-17
AC092718.4	0.522634048	6.61E-30
AC092718.2	0.403216219	2.41E-17
AC092611.2	0.437307672	1.93E-20
AC092611.1	0.409222214	7.29E-18
AC092368.3	0.482365282	4.16E-25
AC092287.1	0.421471195	5.87E-19
AC092171.4	0.428004239	1.47E-19
AC092171.3	0.407500329	1.03E-17
AC092168.2	0.422792841	4.45E-19
AC092123.2	0.412309871	3.90E-18
AC091588.3	0.551756436	8.46E-34
AC091588.1	0.446646584	2.37E-21
AC091057.3	0.415043196	2.23E-18
AC090181.2	0.497425501	7.92E-27
AC087741.1	0.424938813	2.82E-19
AC087588.2	0.476589343	1.81E-24
AC087481.3	0.405881818	1.42E-17
AC087388.1	0.461902531	6.68E-23
AC087071.2	0.40043102	4.17E-17
AC084809.1	0.548988683	2.06E-33
AC084125.2	0.439975116	1.07E-20
AC083923.2	0.498063784	6.66E-27
AC083843.2	0.400474057	4.14E-17
AC083837.1	0.411587047	4.52E-18
AC083799.1	0.40804996	9.22E-18
AC080037.1	0.478174553	1.21E-24
AC079795.1	0.474046845	3.42E-24
AC078883.1	0.498413815	6.06E-27
AC078778.1	0.409147118	7.40E-18
AC074117.1	0.554714176	3.24E-34
AC073957.3	0.48702035	1.25E-25
AC073575.2	0.400138949	4.42E-17
AC073529.1	0.439769623	1.12E-20
AC073335.2	0.443532031	4.81E-21
AC073333.1	0.495110059	1.47E-26
AC073046.1	0.500639796	3.31E-27
AC069544.1	0.425317868	2.60E-19
AC069281.2	0.475165881	2.58E-24
AC068594.1	0.441004287	8.49E-21
AC068580.3	0.533231635	2.80E-31
AC068580.1	0.514898142	6.20E-29
AC068491.3	0.482426646	4.10E-25
AC067930.5	0.501416142	2.68E-27
AC055874.1	-0.48081705	6.19E-25
AC055713.1	0.424519722	3.09E-19
AC046143.1	0.463943799	4.09E-23
AC040162.3	0.400703665	3.96E-17
AC036214.2	0.4332746	4.69E-20
AC027601.1	0.44220419	6.49E-21
AC027514.2	0.403481293	2.29E-17
AC026740.1	0.501958957	2.31E-27
AC026704.1	0.484850458	2.19E-25
AC026471.3	0.416212053	1.75E-18
AC026369.2	0.489854968	5.95E-26
AC026368.1	0.408909281	7.76E-18
AC026362.1	0.434175187	3.85E-20
AC026124.2	0.411297143	4.79E-18
AC025857.2	0.49135673	4.00E-26

AC025580.2	0.403325637	2.36E-17
AC025031.4	0.409910815	6.34E-18
AC024940.5	0.410962557	5.13E-18
AC024560.3	0.417943166	1.23E-18
AC023043.4	0.525391288	2.93E-30
AC023024.1	0.408300889	8.77E-18
AC022762.2	0.400119219	4.44E-17
AC022211.3	0.527934296	1.38E-30
AC022211.2	0.414084821	2.71E-18
AC022211.1	0.522072175	7.79E-30
AC022167.2	0.413251367	3.22E-18
AC022144.1	0.471589544	6.30E-24
AC020922.3	0.470533773	8.18E-24
AC020663.2	0.443171943	5.22E-21
AC020661.1	0.403466344	2.30E-17
AC020656.2	0.451836921	7.19E-22
AC019069.1	0.476275095	1.96E-24
AC018904.1	0.447417673	1.99E-21
AC018695.4	0.441638133	7.37E-21
AC016888.1	0.441462386	7.67E-21
AC016738.1	0.405168071	1.64E-17
AC016737.1	0.40850733	8.41E-18
AC016735.1	0.552145214	7.46E-34
AC016394.1	0.436801565	2.16E-20
AC016065.1	0.429889574	9.78E-20
AC016027.1	0.469553912	1.04E-23
AC015912.3	0.446447501	2.48E-21
AC015849.5	0.546501025	4.55E-33
AC015540.1	-0.420271772	7.55E-19
AC012531.1	0.434378964	3.69E-20
AC012467.1	0.466199946	2.37E-23
AC012363.1	0.477477781	1.44E-24
AC012073.1	0.634263585	3.41E-47
AC012055.1	-0.453672576	4.69E-22
AC011773.3	0.418686986	1.05E-18
AC011747.2	0.463052716	5.07E-23
AC011731.1	0.400755745	3.92E-17
AC011676.1	0.493992466	1.99E-26
AC011476.3	0.407677414	9.94E-18
AC011465.1	0.4263737	2.08E-19
AC010973.2	0.490193784	5.44E-26
AC010761.4	0.567653269	4.32E-36
AC010761.1	0.411357927	4.73E-18
AC010542.5	0.497446099	7.87E-27
AC010503.4	0.680308642	1.30E-56
AC010327.5	0.400969309	3.76E-17
AC009704.2	0.41082487	5.27E-18
AC009495.1	0.411360363	4.73E-18
AC009407.1	0.418326803	1.13E-18
AC009403.1	0.465953946	2.51E-23
AC009133.1	0.500576307	3.37E-27
AC009065.5	0.46097076	8.35E-23
AC009065.2	0.443320215	5.05E-21
AC009061.1	0.52077397	1.14E-29
AC009041.4	0.434718057	3.42E-20
AC009005.1	0.423410013	3.90E-19
AC008915.2	0.439681116	1.14E-20
AC008771.1	0.510463894	2.18E-28
AC008763.1	0.444748775	3.65E-21
AC008760.1	0.423403724	3.91E-19
AC008443.1	0.40657155	1.24E-17
AC008147.2	0.402743866	2.65E-17
AC008115.3	0.424443841	3.14E-19
AC007996.1	0.578019121	1.18E-37
AC007938.2	0.417207609	1.43E-18
AC007639.1	0.485667802	1.78E-25
AC007450.1	-0.414144644	2.68E-18
AC007405.2	0.400899752	3.81E-17

AC007255.1	0.682445582	4.30E-57
AC007128.1	0.404727982	1.79E-17
AC006449.3	0.408486098	8.45E-18
AC006042.1	0.474017049	3.44E-24
AC006007.1	-0.448485832	1.56E-21
AC005726.3	0.405947717	1.40E-17
AC005586.1	0.43178271	6.49E-20
AC005534.1	0.466581171	2.16E-23
AC005288.1	0.418866854	1.01E-18
AC005083.1	0.502106465	2.22E-27
AC005041.3	0.594143501	3.38E-40
AC005037.1	0.508627263	3.65E-28
AC004943.2	0.471783164	6.00E-24
AC004837.2	0.405237294	1.62E-17
AC004596.1	0.493668203	2.17E-26
AC004471.1	0.407008306	1.14E-17
AC004264.1	0.568589776	3.14E-36
AC004241.3	0.434182857	3.85E-20
AC004233.3	0.422336582	4.89E-19
AC004066.2	0.476627219	1.79E-24
AC003965.2	0.537280134	8.12E-32
AC003070.1	0.510273259	2.30E-28
AC002128.2	0.550806243	1.15E-33
AC002128.1	0.414718894	2.38E-18
AC002116.2	0.50477009	1.07E-27
AC000068.1	0.403689678	2.20E-17
ABALON	0.455741964	2.89E-22
INTS4	0.56851767	1.10E-34
ILF3	0.581326784	1.53E-36
IFT52	0.513754303	1.38E-27
HSPA14	0.528879888	2.04E-29
HNRNPU	0.569013357	9.39E-35
HNRNPLL	0.518280793	4.00E-28
HNRNPL	0.564261618	4.40E-34
HNRNPC	0.500290308	4.98E-26
HNRNPA3	0.556480517	5.22E-33
HNRNPA2B1	0.562978859	6.64E-34
HINFP	0.515852892	7.81E-28
HAUS5	0.527476115	3.04E-29
HAT1	0.500155958	5.16E-26
H2AFY	0.563472485	5.67E-34
GTPBP4	0.560686534	1.38E-33
GTF3C3	0.579555378	2.80E-36
GTF3C2	0.586513257	2.56E-37
GTF2H1	0.538295387	1.32E-30
GRPEL2	0.523564163	9.19E-29
GMPS	0.540859325	6.18E-31
FBXO45	0.533964455	4.70E-30
FAM220A	0.508672661	5.45E-27
EWSR1	0.558524823	2.74E-33
EIF2B1	0.551809086	2.23E-32
EFTUD2	0.571810341	3.74E-35
EED	0.502989977	2.46E-26
EDC3	0.544229508	2.25E-31
E2F6	0.614056803	1.10E-41
DYNC1LI1	0.542247298	4.08E-31
DROSHA	0.569793272	7.28E-35
DPF2	0.534240053	4.34E-30
DKC1	0.528663412	2.17E-29
DHX57	0.546758674	1.05E-31
DHX37	0.605151875	3.17E-40
DENR	0.585500037	3.64E-37
DDX27	0.544855951	1.86E-31
DBF4	0.616888974	3.70E-42
DAZAP1	0.536942371	1.97E-30
CWC27	0.535300535	3.18E-30
CSNK2A1	0.536464015	2.26E-30
CSNK1D	0.559093714	2.29E-33

CSE1L	0.522128104	1.37E-28
CPSF6	0.621468842	6.20E-43
COMMD2	0.551600746	2.38E-32
COIL	0.535299778	3.18E-30
CNOT11	0.583078915	8.40E-37
CCT6A	0.58037862	2.11E-36
CCT2	0.557504928	3.78E-33
CCDC97	0.531122135	1.07E-29
CCDC43	0.524334312	7.40E-29
CBX3	0.532933726	6.34E-30
CBX1	0.584182123	5.74E-37
CANT1	0.51881999	3.45E-28
C2orf44	0.553906293	1.17E-32
C12orf65	0.510282371	3.54E-27
BUB3	0.548655675	5.88E-32
BRD9	0.566402981	2.20E-34
BRAP	0.541999944	4.40E-31
BMS1	0.504813409	1.52E-26
ANAPC7	0.572040906	3.47E-35
ANAPC5	0.560741451	1.36E-33
ACTR8	0.519128849	3.17E-28
ACTL6A	0.559771039	1.85E-33
AAAS	0.507175198	8.13E-27
ZNF207	0.866802455	5.21E-119
ZNF195	0.75009316	1.71E-71
XPO5	0.740763007	7.43E-69
WDR75	0.796499478	1.40E-86
VPS54	0.786174554	6.69E-83
UXS1	0.70980749	7.25E-61
UTP6	0.787332538	2.65E-83
UTP18	0.767553764	9.37E-77
USP39	0.826930609	8.49E-99
USP14	0.80076888	3.63E-88
UIMC1	0.830188046	3.02E-100
UBE2Z	0.742653493	2.22E-69
UBE2O	0.764134531	1.09E-75
UBE2N	0.83507824	1.76E-102
UBE2E1	0.805046226	8.58E-90
UBA2	0.83407785	5.12E-102
U2AF2	0.833852515	6.50E-102
TUBD1	0.728618533	1.37E-65
TTC27	0.761364469	7.74E-75
TRMT6	0.771226758	6.39E-78
TRIP4	0.789032558	6.72E-84
TPM3	0.788739441	8.52E-84
TCF3	0.738244466	3.66E-68
SUV39H2	0.805122356	8.02E-90
SUPT7L	0.840562425	4.49E-105
SSRP1	0.83331656	1.15E-101
SRSF2	0.84314263	2.50E-106
SRSF1	0.878494966	3.27E-126
SRRT	0.790165327	2.68E-84
SPDL1	0.788111007	1.42E-83
SPATS2	0.764770371	6.94E-76
SLC26A11	0.719093917	3.78E-63
SFSWAP	0.795968159	2.19E-86
SFPQ	0.857743799	6.95E-114
SET	0.803657503	2.93E-89
SAE1	0.750610774	1.21E-71
RQCD1	0.809285917	1.91E-91
RPIA	0.736150172	1.36E-67
RNF220	0.747436363	9.93E-71
RNF216	0.775123665	3.50E-79
RIC8A	0.772429445	2.63E-78
RHNO1	0.758905424	4.31E-74
RBMX	0.866551362	7.31E-119
RBM45	0.811997566	1.59E-92
RBM17	0.793384688	1.89E-85

RBM14	0.837001915	2.22E-103
RAN	0.771467145	5.35E-78
RALA	0.778500345	2.70E-80
RAD18	0.778274656	3.21E-80
RAD1	0.812574126	9.34E-93
RACGAP1	0.766067705	2.74E-76
R3HDM1	0.793453753	1.79E-85
PWP1	0.772269459	2.96E-78
PTBP1	0.831109339	1.16E-100
PRKAG1	0.804969935	9.18E-90
PRIM2	0.777355033	6.47E-80
PPP1CC	0.770280881	1.28E-77
PPHLN1	0.876780143	4.14E-125
POLR2D	0.749883903	1.97E-71
POLD1	0.73017736	5.34E-66
PGS1	0.799813959	8.28E-88
NUP85	0.7490791	3.36E-71
NUP37	0.78894691	7.20E-84
NKIRAS2	0.723688008	2.59E-64
NCL	0.821570585	1.77E-96
NCBP2	0.78588425	8.43E-83
NAT10	0.799903582	7.67E-88
NAP1L4	0.757878946	8.77E-74
MTA3	0.725600152	8.34E-65
MRPL42	0.814400163	1.70E-93
MMS19	0.764763719	6.97E-76
MGME1	0.831806826	5.60E-101
METTL6	0.788614258	9.43E-84
MCRS1	0.706383166	4.79E-60
MCM6	0.739783062	1.38E-68
MAPKAPK5	0.852893456	2.77E-111
KHDRBS1	0.851743025	1.11E-110
INTS4	0.790165564	2.68E-84
ILF3	0.832883845	1.81E-101
IFT52	0.727453831	2.76E-65
HSPA14	0.82801655	2.81E-99
HNRNPU	0.885485685	6.98E-131
HNRNPLL	0.828336686	2.03E-99
HNRNPL	0.886060908	2.79E-131
HNRNPC	0.870487724	3.34E-121
HNRNPA3	0.850688092	3.93E-110
HNRNPA2B1	1	0
HINFP	0.759337403	3.19E-74
HAUS5	0.759381632	3.10E-74
HAT1	0.797111047	8.33E-87
H2AFY	0.760362256	1.56E-74
GTPBP4	0.793014293	2.58E-85
GTF3C3	0.827860197	3.30E-99
GTF3C2	0.829989353	3.71E-100
GTF2H1	0.78963031	4.14E-84
GRPEL2	0.741739547	3.98E-69
GMPS	0.831848874	5.36E-101
FBXO45	0.760604075	1.32E-74
FAM220A	0.778644222	2.42E-80
EWSR1	0.863258274	5.83E-117
EIF2B1	0.814974585	9.93E-94
EFTUD2	0.769919288	1.67E-77
EED	0.778894336	1.99E-80
EDC3	0.737167123	7.19E-68
E2F6	0.813380883	4.41E-93
DYNC1LI1	0.739644509	1.51E-68
DROSHA	0.818669424	2.96E-95
DPF2	0.779368777	1.38E-80
DKC1	0.787614013	2.11E-83
DHX57	0.784667897	2.21E-82
DHX37	0.738950033	2.34E-68
DENR	0.79370584	1.45E-85
DDX27	0.751052479	9.05E-72

DBF4	0.782877677	9.07E-82
DAZAP1	0.762887861	2.65E-75
CWC27	0.808417064	4.20E-91
CSNK2A1	0.768111356	6.26E-77
CSNK1D	0.78935007	5.19E-84
CSE1L	0.760834722	1.12E-74
CPSF6	0.87233179	2.51E-122
COMMD2	0.801922961	1.33E-88
COIL	0.808319246	4.58E-91
CNOT11	0.726856362	3.95E-65
CCT6A	0.795196287	4.18E-86
CCT2	0.802842487	5.98E-89
CCDC97	0.739301957	1.88E-68
CCDC43	0.786795802	4.07E-83
CBX3	0.846069822	8.83E-108
CBX1	0.839385981	1.65E-104
CANT1	0.713776982	7.86E-62
C2orf44	0.75093213	9.80E-72
C12orf65	0.753500519	1.75E-72
BUB3	0.824603751	8.81E-98
BRD9	0.743209489	1.55E-69
BRAP	0.784253071	3.07E-82
BMS1	0.802139952	1.10E-88
ANAPC7	0.733701841	6.19E-67
ANAPC5	0.770726405	9.25E-78
ACTR8	0.735915259	1.57E-67
ACTL6A	0.837573905	1.20E-103
AAAS	0.778070306	3.75E-80

4.5. HOTAIR/miR-206 Sponge Regulated SOX9 in GC

The HOTAIR/miR-206/SOX9 axis was identified in the ceRNA analysis. Based on the TCGA datasets, the expression of HOTAIR was up-regulated in GC tumor tissues compared with normal tissues and was positive correlated with the expression of SOX9 (Figure 6a). The *q*RT-PCR also showed that the HOTAIR expression level was significantly increased in GC cell lines than in normal cell lines, particularly in MKN45 and HGC-27, and had a significantly positive correlation with the expression of SOX9 (Figure 6b). Next, three siRNAs (siRNA #1-#3) against HOTAIR were transfected into MKN45 and HGC-27 cells. As the *q*RT-PCR shows, siRNA#2 formed the maximal decreasing of HOTAIR expression (Figure 6c), so siRNA#2 was chosen for further experiments. Knockdown of HOTAIR significantly decreased GC cell growth measured with CKK8 assay (Figure 6d). The survival rate of MKN45 and HGC-27 cells was down-regulated after disposed of with siRNA#2 compared to the negative control (NC). These results showed that HOTAIR knockdown has the potential to inhibit cell proliferation. Meanwhile, the decreasing expression of SOX9 and the increasing miR-206 were shown in si-HOTAIR compared with NC (Figure 6e).

Furthermore, to examine the function of HOTAIR in the initiation and progression of GC, we investigated miRNAs by bioinformatics analysis. According to microRNA.org (http://www.microrna.org/microrna/home.d) and ChipBase v2.0 (http://rna.sysu.edu.cn/chipbase/), as shown in (Figure 6f), HOTAIR includes a putative binding site for miR-206. Transfection of MKN45 and HGC-27 cells with miR-206-mimic significantly reduced the expression of SOX9 compared with the NC (Figure 6g). While miRNAs are known to target specific genes to regulate cancer progression, to identify putative target genes of miR-206 we searched for candidate genes by using Target Scan Human 7.1 software (http://www.targetscan.org/vert_72/). Bioinformatics analysis predicted that miR-206 contains a putative binding site for the SOX9 3'UTR (Figure 6f). Next, we constructed luciferase reporter vectors containing the HOTAIR-WT or HOTAIR-mut. The luciferase reporter assay results showed co-transfection cells with HOTAIR-WT vector and miR-206-mimic significantly inhibited luciferase reporter activity, but miR-206-inhibitor up-regulated the luciferase activity of HOTAIR. While HOTAIR-mut in the putative targeting sites of miR-206 did not result in these effects (Figure 6h). Then, luciferase reporter vectors containing the 3'UTR of SOX9 or 3'UTR of SOX9 mut were also constructed. The luciferase reporter assay results showed co-transfection cells with SOX9-WT vector and miR-206-mimic significantly inhibited luciferase reporter activity, but miR-206-inhibitor up-regulated the luciferase activity. Still, SOX9-mut in the putative targeting sites of miR-206 did not result in these effects (Figure 6h).

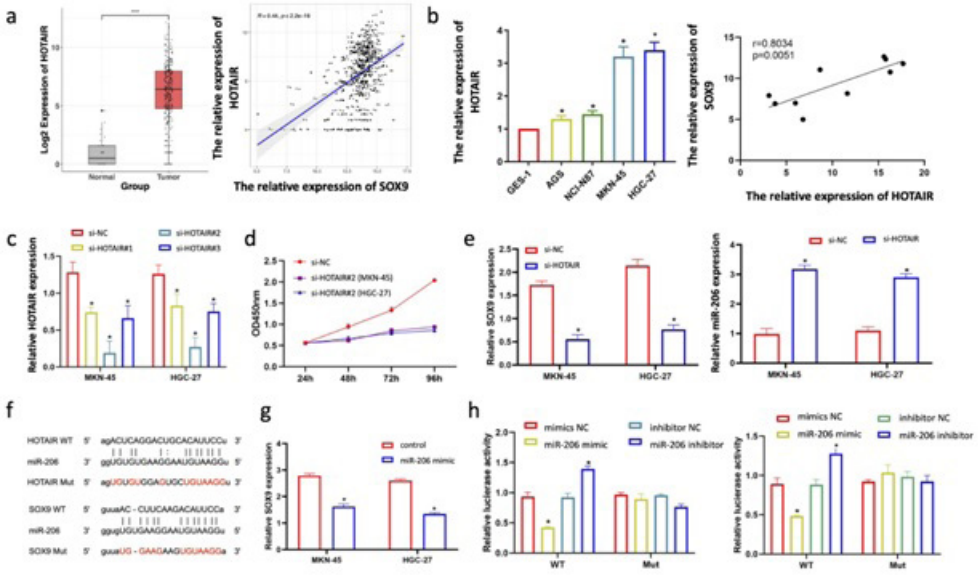

Figure 6: HOTAIR/miR-206/SOX9 axis in GC cell line. This relative expression of HOTAIR and correlation with SOX9 in TCGA datasets(a) and GC cell lines AGS, NCI-N87, MKN-45, HGC-27 and a normal gastric epithelium cell line GES-1 (b), respectively. The expression levels of HOTAIR in cell lines were normalized to GAPDH. (c) The efficiency of HOTAIR siRNA transfection in MKN-45 and HGC-27. (g) The nucleotide alignment between miR-206 with wild type HOTAIR wild type SOX9. (h) The effect of miR-206 over expression on expression of HOTAIR (left) and SOX9(right), respectively. „p<0.05.

5. Discussion

As a worldwide high incidence tumor, gastric cancer has attracted much attention. As we all know, the mechanism of gastric cancer is a multigene and multi-step process. It's essential to study the occurrence and development of these genes. In this study, we clarify the expression and function of the SOX genes in tumorigenesis of gastric cancer based on the TCGA datasets, established a ceRNA network mediated by the SOX genes, investigated the biological processes of DEGs regulated by SOX9, and validated the function of HOTAIR/miR-206/SOX9 axis in GC cell lines.

In total 19 SOX genes, we found seven genes differentially expressed in GC tumor tissues compared with normal tissues. Then, the ceRNA network consisting of 64 lncRNAs, 29 miRNAs, and 11 SOX genes was constructed. Among five differentially expressed SOX genes in the ceRNA network, SOX9 was shown specifically in GC, and identified as highly expressed in the gastrointestinal tract. Thus, SOX9 was considered a critical factor in GC tumorigenesis. The median value of its expression levels was applied as a cut-off to divide GC samples into high- and low-level groups, 50 DEGs were identified which might be regulated by SOX9. Biological enrichment analysis suggested that SOX9 might influence the genes related to the pattern specification process, sodium ion homeostasis, and potassium ion transport, mainly including FEZF1, HOXC13, HOXC10, HOXC9, HOXA11, DPP6, ATP4B, CASQ2, KCNA1, ATP4A, and SFRP1.

As we all know, the regulatory relationships existed between miRNAs and lncRNAs, particularly for the transcripts from miRNAs of the host genes. Previous studies suggested that miRNAs act as oncogenes or cancer suppressors in various carcinomas. The long noncoding RNA homeobox (HOX) transcript antisense intergenic RNA (HOTAIR) has been demonstrated to be a vital modulator in various aspects of cellular homeostasis, such as proliferation, cell cycle progression, migration and invasion of several cancer cells, including lung cancer, cervical cancer, breast cancer, ovarian cancer, etc. [35]. HOTAIR/miR-206 sponge was identified regulating different genes. HOTAIR relieved the inhibition of TBX3 expression mediated by miR-206 in ovarian cancer stem cells [36, 37]. HOTAIR regulated head and neck squamous cell carcinoma cell biological functions by binding to miR-206 through STC2 [38, 39]. HOTAIR plays as an oncogene via directly sponging miR-206 to activate the downstream CCL2 in colorectal cancer [40]. HOTAIR affects the expression of OATP1B1, which is an important drug transporter with a complex regulatory mechanism in HepG2 cells by sponging miR-206/miR-613 [41]. HOTAIR promotes medulloblastoma progression via acting as a competing endogenous RNA (ceRNA) to regulate YY1 expression through binding to miR-1 and miR-206 [42]. miR-206 was also found to affect invasion, proliferation, and metastasis by targeting SOX9 in hepatocellular carcinoma, and triple negative breast cancer [43, 44]. However, no evidence shown HOTAIR/miR-206 sponge regulated SOX9 in tumorigenesis, which was identified in our study of the ceRNA network analysis. We found that miR-206 could be negatively regulated by HOTAIR, which knockdown of HOTAIR was the potential to inhibit cell proliferation, while miR-206 could negatively regulate SOX9. These results indicated that HOTAIR could induce proliferation potentially by competitively binding miR-206/SOX9 axis in GC.

6. Conclusion

In this study, we identified the function of SOX genes participating in GC tumorigenesis. We constructed the ceRNA network mediated

by the SOX genes. SOX9 was shown specifically in GC tumor tissues and identified as highly expressed in the gastrointestinal tract. We also found the HOTAIR/miR-206/SOX9 axis might be critical in GC tumorigenesis. HOTAIR positively regulated GC cell by targeting miR-206/SOX9 axis. The application of HOTAIR/miR-206/SOX9 axis to the treatment of GC will be investigated in future studies.

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