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Association of lncRNA SOX2OT rs9839776 polymorphism with gastric cancer risk in Korean
Case-control study

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Abstract

Aberrant regulation of the long non-coding RNA SRY-box transcription factor 2 overlapping transcript (*SOX2OT*) has been reported in various diseases including gastric cancer (GC). However, an association between the well-studied rs9839776 single nucleotide polymorphism in *SOX2OT* and GC susceptibility has not been reported. This study aimed to evaluate the association between the rs9839776 single nucleotide polymorphism in *SOX2OT* and GC risk. Genotyping of rs9839776 was conducted using TaqMan genotyping assay for 460 patients with GC and 386 controls. We found that the dominant model (CT+TT) and rs9839776 T allele were significantly associated with decreased GC risk ($P = .046$, adjusted odds ratio [AOR] = 0.72, 95% confidence interval [CI] = 0.52–1.00 and $P = .044$, AOR = 0.74, 95% CI = 0.56–0.99, respectively). In addition, stratified analysis revealed that the dominant model (CT+TT) and rs9839776 T allele were significantly associated with decreased risk of lymph node metastasis-negative ($P = .039$, AOR = 0.67, 95% CI = 0.46–0.98 and $P = .049$, AOR = 0.71, 95% CI = 0.51–1.00, respectively) and tumor stage I (A+B)/II (A+B+C) ($P = .028$, AOR = 0.66, 95% CI = 0.50–0.96 and $P = .041$, AOR = 0.71, 95% CI = 0.52–0.99, respectively) GC. Our findings suggest that the rs9839776 T allele may be a protective factor against GC susceptibility. Further research is needed to clarify whether rs9839776 affects *SOX2OT* expression.

Abbreviations: AOR = adjusted odds ratio, BC = breast cancer, CI = confidence interval, GC = gastric cancer, lncRNA = long non-coding RNA, LNM = lymph node metastasis, SNP = single nucleotide polymorphism, SOX2OT = SRY-box transcription factor 2 overlapping transcript.

Keywords: cancer risk, gastric cancer, LncRNA, single nucleotide polymorphism, SOX2OT

1. Introduction

Long non-coding RNAs (lncRNAs) are defined as non-translated RNAs that are longer than 200 nucleotides. Although they do not encode proteins, lncRNAs play important roles in several human diseases through post-transcriptional regulation. In cancer, lncRNAs contribute to tumorigenesis by regulating cell proliferation, invasion, and metastasis.[1–3] Given their role in tumorigenesis, lncRNAs are potential diagnostic biomarkers of cancer because they are present not only in cells but also in bodily fluids, such as serum, plasma, urine, and saliva.[4]

The lncRNA SRY-box transcription factor 2 overlapping transcript (*SOX2OT*) is located on human chromosome 3q26.3 and the *SOX2*, a regulator of pluripotency, is present in the intronic region of *SOX2OT*.[5,6] Recently, aberrant expression of *SOX2OT* has been reported to be associated with the progression of various cancers, such as breast cancer (BC), gastric cancer (GC), colorectal cancer, esophageal squamous cell carcinoma, ovarian cancer, non-small cell lung cancer, and hepatocellular carcinoma. According to accumulation studies, upregulation of both *SOX2* and *SOX2OT* has been observed in estrogen receptor-positive BC compared to that in estrogen

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

The study was performed in line with the principles of the Declaration of Helsinki and approved by the ethics committee of the institutional review board of Chungnam National University Hospital.

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receptor-negative BC.[7] Overexpression of *SOX2OT* has been reported in both GC tissues and cell lines.[8,9] Another study reported that *SOX2OT* overexpression promotes GC progression by sponging miR-149-5p.[10] In addition, high expression of *SOX2OT* has been reported in several cancers, such as colorectal cancer, esophageal squamous cell carcinoma, OC, non-small cell lung cancer, and hepatocellular carcinoma.[11–15]

According to genome-wide association studies, more than 90% of disease-associated single nucleotide polymorphisms (SNPs) occur in non-coding regions, such as regulatory regions, intronic and intergenic regions, and non-coding RNA.[16,17] Polymorphisms in the regulatory regions of lncRNAs affect their expression.[18,19] According to the GLOBOCAN 2020 estimates, GC is one of the most common cancers and the fourth leading cause of cancer deaths worldwide.[20] Recently, polymorphisms in several lncRNAs, such as plasmacytoma variant translocation 1, HOX antisense intergenic RNA, and metastasis-associated lung adenocarcinoma transcript 1, have been reported to be associated with GC susceptibility.[21–24]

Although many studies have investigated the relationship between abnormal expression of *SOX2OT* and various diseases, including GC, few studies have demonstrated a relationship between the rs9839776 SNP in *SOX2OT* and diseases. rs9839776 was first reported to be related to anorexia nervosa in a genome-wide association studies comprising of 2907 patients with anorexia nervosa and 14,860 healthy controls.[25] Subsequently, a few studies reported that rs9839776 is associated with increased risk of BC and miscarriage, and decreased risk of sepsis.[26–28]

Base on previous studies, we firstly evaluated the association between rs9839776 and GC susceptibility. Additionally, we evaluated the association between rs9839776 and GC clinical features, such as tumor differentiation, histological type, T classification, lymph node metastasis (LNM), and tumor stage.

2. Material and methods

2.1. Study participants

Peripheral blood samples were obtained from 460 patients with GC and 386 cancer-free controls. All samples used in this study were provided by the Chungnam National Hospital Biobank, a member of the National Biobank of Korea, which is supported and audited by the Ministry of Health and Welfare of Korea. Patients with GC were recruited from the outpatient clinic at Chungnam National University Hospital and classified according to Lauren's classification.[29] The cancer-free control subjects were randomly selected from healthy volunteers visiting the Chungnam National University Hospital Medical Center; only individuals who had no history of cancer were included.

Informed consent was obtained from all study participants. This study was approved and reviewed by the Ethics Committee of the Institutional Review Board of Chungnam National University Hospital.

2.2. DNA isolation and genotyping

Genomic DNA was obtained from peripheral blood samples using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instructions. Genotyping was performed with the Applied Biosystems TaqMan SNP Genotyping Assay (Waltham, MA) using predesigned primer/probe sets (C_42766292_10; Applied Biosystems) and the StepOnePlus Real-time PCR System (Applied Biosystems), at the following cycling conditions: 1 cycle at 95 °C for 10 minutes followed by 45 cycles at 92 °C for 15 seconds and 60 °C for 90 seconds.

2.3. Statistical analysis

Differences in age and sex between the GC and control groups were calculated using the 2-sided Pearson chi-square test and the Mann–Whitney *U* test. Hardy–Weinberg equilibrium for rs9839776 in the control groups was estimated using the chi-square test. Four genetic models, including the codominant (CT or TT vs CC), dominant (CT+TT vs CC), recessive (TT vs CC+CT), and allelic (C vs T) models, were used to analyze the associations. Binary logistic regression was used to estimate GC risk based on the odds ratio and 95% confidence interval (CI). The association analysis was adjusted for age and sex, which were included in the model as covariates. All statistical analyses were performed using SPSS version 26.0 for Windows (IBM, Armonk, NY). $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics of the study participants

The characteristics of the 460 patients with GC and 386 cancer-free controls included in the present study are summarized in Table 1. There were statistically significant differences in age and sex between the GC and control groups ($P < .001$ and $P < .001$, respectively). The mean age was 64.9 ± 10.7 years for the GC group and 56.6 ± 9.9 years for the control group. The percentage of male participants (70.4%) was higher than that of female participants (29.6%) in the GC group, whereas the percentage of female participants (67.6%) was higher than that of male participants (32.4%) in the control group. Majority of patients with GC had the following clinical features: differentiated tumor (48.3%), intestinal type (56.1%), T1 (50.7%), LNM negative (62.0%), and tumor stage I (59.1%).

Table 1

Characteristics and clinical features of the gastric cancer group and the control group.

Variables	Gastric cancers, N (%)	Controls, N (%)	*P*
Age (yr) (mean ± SD)	460 (64.9 ± 10.7)	386 (56.6 ± 9.9)	<.001*
<60	198 (52.4 ± 5.9)	200 (49.2 ± 5.6)	.011†
≥60	262 (70.9 ± 6.4)	186 (65.9 ± 4.4)	
Gender (%)			
Male	324 (70.4)	125 (32.4)	<.001†
Female	136 (29.6)	261 (67.6)	
Tumor differentiation (%)			
Differentiated	222 (48.3)		
Undifferentiated	197 (42.8)		
Missing	41 (8.9)		
Histological type (%)			
Intestinal	258 (56.1)		
Diffuse	148 (32.2)		
Mixed	54 (11.7)		
T classification (%)			
T1	233 (50.7)		
T2	67 (14.6)		
T3	20 (4.3)		
T4	140 (30.4)		
Lymph node metastasis (%)			
Negative	285 (62.0)		
Positive	175 (38.0)		
Tumor stage (%)			
I (A+B)	272 (59.1)		
II (A+B)	54 (11.8)		
III (A+B+C)	134 (29.1)		

SD = standard deviation.

*Mann–Whitney *U* test.

†Two-sided Pearson chi-square test.

3.2. Association of rs9839776 with GC risk

We genotyped the rs9839776 SNP in *SOX2OT* to determine its relevance to GC risk, which has been previously reported in diseases, including BC. The distribution of rs9839776 in the control group was in Hardy–Weinberg equilibrium (P = .922). We applied 4 genetic models to evaluate the possible association between rs9839776 and GC risk. After adjusting for age and sex, the rs9839776 CT+TT genotype showed a significant association with decreased GC risk compared with the CC genotype (P = .046, adjusted odds ratio [AOR] = 0.72, 95% CI = 0.52–1.00) in the dominant model. Additionally, the rs9839776 T allele showed a significant association with decreased GC risk compared with the rs9839776 C allele (P = .044, AOR = 0.74, 95% CI = 0.56–0.99) (Table 2).

Table 2

Genotype and allele frequencies for *SOX2OT* rs9839776 polymorphism among subjects and their association with GC risk.

		GC vs CON		
Genotype	**CON, N (%)**	**N (%)**	**AOR (95% CI)***	***P****
Codominant				
CC	265 (68.7)	349 (75.9)	1	
CT	111 (28.7)	102 (22.2)	0.73 (0.52-1.02)	.066
TT	10 (2.6)	9 (1.9)	0.61 (0.23-1.62)	.317
Dominant				
CC	265 (68.7)	349 (75.9)	1	
CT+TT	121 (31.3)	111 (24.1)	0.72 (0.52-1.00)	**.046**
Recessive				
CC+CT	376 (97.4)	451 (98.1)	1	
TT	10 (2.6)	9 (1.9)	0.66 (0.23-1.75)	.401
Alleles				
C	641 (83.0)	800 (87.0)	1	
T	131 (17.0)	120 (13.0)	0.74 (0.56-0.99)	**.044**
HWE	0.922	0.890		

The significant results are in bold.

AOR = adjusted odds ratio, CI = confidence interval, CON = control, GC = gastric cancer, HWE = Hardy–Weinberg equilibrium.

*Adjusted for age and gender.

3.3. Stratified analysis for rs9839776

Furthermore, we performed stratified analysis according to tumor differentiation, histological type, LNM, T classification, and tumor stage (Table 3). After adjusting for age and sex, the rs9839776 CT+TT genotype showed a significant association with decreased GC risk in the LNM-negative and tumor stage I (A+B)/II (A+B+C) subgroups compared with the rs9839776 CC genotype (P = .039, AOR = 0.67, 95% CI = 0.46–0.98 and P = .028, AOR = 0.66, 95% CI = 0.50–0.96, respectively) in the dominant model. Furthermore, the rs9839776 T allele showed a significant association with decreased GC risk in the LNM-negative and tumor stage I (A+B)/II (A+B+C) subgroups compared with the rs9839776 C allele (P = .049, AOR = 0.71, 95% CI = 0.51–1.00 and P = .041, AOR = 0.71, 95% CI = 0.52–0.99, respectively).

4. Discussion

Previous studies have elucidated that abnormal upregulation of *SOX2OT* affects cancer development and progression.[7–15] The rs9839776 SNP in *SOX2OT* is a pathogenic SNP that has been reported to be related to anorexia nervosa, BC, miscarriage, and sepsis.[25–28] However, even though *SOX2OT* overexpression has been reported to promote GC progression,[10] the association between rs9839776 and GC susceptibility has not been clarified. Therefore, in the present study, we evaluated the association between rs9839776 and GC susceptibility. Consistently, we found that the dominant model (CT+TT) of rs9839776 was significantly associated with decreased risk of GC (1.39 times) and LNM-negative and tumor stage I (A+B)/II (A+B+C) GC (1.49 and 1.52 times, respectively).

Qu and Cao[10] reported that *SOX2OT* acts as a sponge for mir-194-5p in GC and contributes to its progression by regulating the expression of AKT serine/threonine kinase 2. Song et al[30] elucidated that knockdown of *SOX2OT* inhibits prostate cancer growth by regulating the expression of high mobility group box 3 via sponging of miR-452-5p. Further, Zou et al[9] reported that *SOX2OT* expression is associated with T stage and differentiation, but not with LNM, in GC, and that *SOX2OT* overexpression is also associated with poor overall survival. However, in the present study, we did not assess whether the rs9839776 SNP affects *SOX2OT* expression.

Table 3

Stratified analysis of *SOX2OT* rs9839776 polymorphism and GC risk.

	GC vs CON							
	Dominant (CT+TT/CC)				Allele (T/C)			
Variables	**GC**	**CON**	**OR (95% CI)***	***P****	**GC**	**CON**	**OR (95% CI)***	***P****
Tumor differentiation								
Differentiated	53/169	121/265	0.73 (0.48–1.11)	.140	56/388	131/641	0.72 (0.49–1.04)	.082
Undifferentiated	49/148	121/265	0.75 (0.50–1.13)	.164	55/339	131/641	0.81 (0.57–1.15)	.240
Histological type								
Intestinal	35/113	121/265	0.77 (0.52–1.15)	.206	38/258	131/641	0.76 (0.53–1.08)	.127
Diffuse	64/194	121/265	0.69 (0.44–1.08)	.106	68/448	131/641	0.73 (0.49–1.09)	.125
LNM								
Negative	66/219	121/265	0.67 (0.46–0.98)	**.039**	72/498	131/641	0.71 (0.51–1.00)	**.049**
Positive	45/130	121/265	0.79 (0.51–1.20)	.267	48/302	131/641	0.79 (0.54–1.15)	.211
T classification								
T1/T2	70/230	121/265	0.70 (0.48–1.02)	.060	77/523	131/641	0.74 (0.53–1.03)	.077
T3/T4	41/119	121/265	0.77 (0.49–1.20)	.249	43/277	131/641	0.76 (0.51–1.13)	.173
Tumor stage								
I (A+B)/II (A+B+C)	74/251	121/265	0.66 (0.50–0.96)	**.028**	82/568	131/641	0.71 (0.52–0.99)	**.041**
III (A+B+C)	37/98	121/265	0.86 (0.54–1.36)	.509	38/232	131/641	0.81 (0.53–1.22)	.312

The significant results are in bold.

AOR = adjusted odds ratio, CI = confidence interval, CON = controls, GC = gastric cancer.

*Adjusted by age and gender.

In our present study, we showed that rs9839776 is related with decreased GC risk. In contrast to our results, Tang et al[26] reported that rs9839776 is significantly associated with high *SOX2OT* expression and increased risk of BC (1.43 times). In stratified analysis, they observed that the dominant model (CT+TT) is associated with increased risk of the following BC subgroups: moderate differentiation and T2 tumor stage. Furthermore, Fang et al[27] reported that the rs9839776 CT genotype is associated increased risk of recurrent miscarriage (1.36 times). Consistent with our results, Wu et al[28] demonstrated that the dominant model (CT+TT) of rs9839776 SNP is related with 1.29 times decreased risk of sepsis. Given the different risk results for each disease, it is speculated that the rs9839776 variation may affects different disease in different ways.

This case–control study had a few limitations. First, the sample size was too small to assess the impact of stratified analysis on statistical power. Second, the proportion of age and sex in the GC and control groups was imbalanced. Thus, we adjusted for age and sex as confounders in the binary logistic regression analysis. Third, we did not evaluate the relationship between rs9839776 and other clinical features of GC, such as drinking, smoking, and Helicobacter pylori infection. Finally, our findings should be validated in other ethnic groups.

In conclusion, our findings suggest that the rs9839776 T allele may be a protective factor against GC susceptibility and may hence contribute to GC development. Further studies are needed to confirm our findings in a larger population and with different ethnic groups and to verify whether rs9839776 affects *SOX2OT* expression.

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Author contributions

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