





Association Between lncRNA HULC rs7763881 Polymorphism and Gastric Cancer Risk

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Purpose: Gastric cancer (GC) is one of the most common cancers in the world. Recently, several studies have suggested that single-nucleotide polymorphisms (SNPs) of long non-coding RNA (lncRNA) are associated with GC risk. However, the association of the lncRNA highly upregulated in liver cancer (*HULC*) SNP with GC risk is not yet known. The aims of this study were to evaluate the association between *HULC* rs7763881 SNP and the risk of GC and GC subgroups via a case-control study.

Patients and Methods: rs7763881 was genotyped using TaqMan genotyping assay with 459 GC patients and 379 controls.

Results: A significant association between *HULC* rs7763881 SNP and GC risk was not found. However, after adjustment for age and gender, the rs7763881 recessive model (CC) showed a significant association with an increased GC risk in the undifferentiated (odds ratio (OR) = 1.85, 95% confidence interval (CI) = 1.17–2.94, $P = 0.009$), diffuse-type GC (OR = 1.72, 95% CI = 1.05–2.82, $P = 0.033$), LNM-positive (OR = 2.02, 95% CI = 1.24–3.27, $P = 0.004$), T3/T4 (OR = 1.75, 95% CI = 1.05–2.91, $P = 0.032$), and tumor stage III (OR = 2.01, 95% CI = 1.17–3.45, $P = 0.011$) subgroups when compared to the rs7763881 combined genotypes (AA+AC). Furthermore, after adjusting for age and gender, the rs7763881 additive model (CC) indicated a significantly higher GC risk than rs7763881 AA genotype in the undifferentiated (OR = 1.96, 95% CI = 1.15–3.32, $P = 0.013$), diffuse-type GC (OR = 2.08, 95% CI = 1.23–3.52, $P = 0.004$), and LNM-positive (OR = 2.00, 95% CI = 1.14–3.49, $P = 0.016$) subgroups.

Conclusion: Our findings suggest that the *HULC* rs7763881 SNP is associated with increased susceptibility to GC. However, further studies are required to validate our results in large populations as well as different ethnic groups.

Keywords: lncRNA, HULC, gastric cancer, polymorphism

Introduction

Gastric cancer is one of the most common cancers worldwide and the fourth most common cancer with high mortality in South Korea in 2015. Gastric cancer (GC) incidence remains high in Asian countries despite its global decrease over the past few years.^{1,2}

Long noncoding RNAs (lncRNAs) are defined as non-coding transcripts with lengths > 200 nucleotides.³ In recent years, a number of studies have demonstrated that non-coding RNAs, such as lncRNAs, are implicated in cancer development through regulation of cancer-related gene expression, thus acting as oncogenes and tumor suppressors in several cancers.⁴ lncRNAs including H19 imprinted maternally expressed transcript (H19),^{5,6} HOX transcript antisense RNA (HOTAIR),^{7,8} colon cancer-associated transcript 2 (CCAT2),^{9,10} Pvt1 oncogene (PVT1),^{11,12} and

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metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)^{13,14} have been reported as oncogenes that are upregulated in gastric cancer. However, lncRNAs including maternally expressed 3 (MEG 3)^{15,16} and growth arrest-specific 5 (GAS5)¹⁷ have demonstrated as tumor suppressors that were downregulated in gastric cancer. LncRNA highly up- have been demonstrated as tumor suppressors that are downregulated in gastric cancer. The lncRNA highly upregulated liver cancer (*HULC*) gene, located on chromosome 6p24.3, has a length of 1638 bp and comprises two exons and one intron. *HULC* has been reported as an oncogene that is upregulated in several cancers, including hepatocellular carcinoma (HCC),¹⁸ gastric cancer,¹⁹ pancreatic cancer,²⁰ osteosarcoma,²¹ glioma²² and ovarian cancer.²³ Additionally, recent studies have reported that genetic variations in *HULC* are associated with susceptibility to various cancers. For instance, in Chinese populations, Liu et al reported the association between *HULC* rs7763881 SNP and decreased HCC risk,²⁴ and Kang et al reported the association between *HULC* rs7763881 SNP and decreased esophageal squamous cell carcinoma (ESCC) risk.²⁵ In Egyptian populations, Shaker et al reported the association between *HULC* rs7763881 SNP and decreased colorectal cancer (CRC) risk,²⁷ and Motawi et al reported the association between *HULC* rs7763881 SNP and decreased HCC risk.²⁶ However, the association between *HULC* rs7763881 SNP and GC risk is not yet reported.

Based on previous study, we hypothesized *HULC* rs7763881 SNP may contribute to susceptibility to GC. Therefore, we investigated the association between *HULC* rs7763881 SNP and GC risk in a Korean population. We further evaluated the correlation of *HULC* rs7763881 SNP with clinical features, including age, gender, tumor differentiation, histological type, LNM, T classification, and tumor stage.

Patientss and Methods

Study Subjects

This study was approved and reviewed by the Ethics Committee of the institutional review board of Chungnam National University Hospital, and in compliance with the Declaration of Helsinki. A total of 459 GC subjects and 379 control subjects were enrolled. The blood samples used in this study were provided by the Chungnam National University Hospital Biobank, a member of the National Biobank of Korea, which is supported and audited by the Ministry of

Health and Welfare of Korea. All individuals enrolled in this study provided written informed consent for blood collection and use. GC patients were recruited from the outpatient clinic at the Chungnam National University Hospital and classified according to Lauren's classification.²⁸ The subjects for the control group were randomly selected among healthy volunteers visiting the Chungnam National University Hospital medical center for their annual physical examinations; only individuals who had no history of cancer were included.

DNA Isolation and Genotyping

Genomic DNA was isolated from peripheral blood samples of all subjects using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany), according to the manufacturer's instructions. *HULC* rs7763881 SNP was genotyped by the Applied Biosystems TaqMan SNP Genotyping Assay using predesigned primer/probe sets (C_29335152_10). PCR was performed using the StepOnePlus Real-time PCR System (Applied Biosystems) according to the following conditions: one cycle at 95 °C for 10 min; 45cycles at 92 °C for 15 s and 60 °C for 90 s.

Statistical Analysis

Hardy Weinberg equilibrium (HWE) for each SNP in the control groups was estimated using the chi-square test. Differences in age and gender between the GC and control groups were calculated using the two-sided Pearson chi-square test and the Mann–Whitney *U*-test. Five genetic models, including codominant (CC or AC vs AA), dominant (AC +CC vs AA), recessive (CC vs AA+AC), additive (CC vs AA), and allelic (C vs A) models, were used to analyze the associations. A binary logistic regression was used to estimate the GC risk according to odds ratios (ORs) and 95% confidence intervals (CIs). The association analysis was adjusted by age and sex, which were included in the model as covariates. All statistical analyses were performed using the SPSS (SPSS Inc., Chicago, IL, USA), version 20.0 for Windows. $P < 0.05$ was considered statistically significant.

Results

Characteristics of Study Subjects

The characteristics of 459 GC and 379 control subjects are summarized in Table 1. There were statistically significant differences in the age and gender distribution between the two groups ($P < 0.001$ and $P < 0.001$, respectively). The mean age was 65.2±10.6 years for GC patients and 56.1±10.9 years for the controls. The percentage of GC male subjects (70.2%) was

Table 1 Demographic and Clinical Features of the Gastric Cancer Group and the Control Group

Variables	Gastric Cancers	Controls	P
	N (%)	N (%)	
Age (years) (mean±SD)	459 (65.2±10.6)	379 (56.1±10.9)	<0.001*
<60	197 (42.9)	195 (51.5)	0.014**
≥60	262 (57.1)	184 (48.5)	
Gender (%)			<0.001**
Male	322 (70.2)	121 (31.9)	
Female	137 (29.8)	258 (68.1)	
Tumor Differentiation (%)			
Differentiated	222 (48.4)		
Undifferentiated	196 (42.7)		
Missing	41 (8.9)		
Histological Type (%)			
Intestinal	258 (56.2)		
Diffuse	148 (32.2)		
Mixed	53 (11.6)		
T Classification (%)			
T1	234 (51.0)		
T2	67 (14.6)		
T3	16 (3.5)		
T4	142 (30.9)		
Lymph Node Metastasis (%)			
Negative	286 (62.3)		
Positive	173 (37.7)		
Tumor Stage (%)			
I (A+B)	275 (59.9)		
II (A+B)	55 (12.0)		
III (A+B+C)	129 (28.1)		

Notes: *Mann-Whitney U-test. **Two-sided Pearson chi-square test.

Abbreviation: SD, standard deviation.

higher than that of females (29.8%), whereas the number of female control subjects (68.1%) was higher than that of males (31.9%). The GC group consisted of 48.4% well-differentiated GC, 56.2% intestinal-type, 51.0% T1, 62.3% lymph node metastasis, and 59.9% stage I tumor cases.

Association of SNP and GC Risk

We genotyped rs7763881 SNP in *HULC*, which has been previously associated with cancer risk. The genotype distribution of rs7763881 SNP, both among the GC group and the control group, was in accordance with HWE ($P = 0.998$ and $P = 0.373$, respectively). We applied five genetic models to assess the possible association between the rs7763881 SNP and GC risk. However, no significant association between rs7763881 SNP and GC risk was observed (Table 2).

Table 2 Genotype and Allele Frequencies for *HULC* rs7763881 Polymorphism Among Subjects and Their Association with GC Risk

Genotype	CON	GC vs CON		
	N (%)	N (%)	AOR (95% CI) ^a	P ^a
rs7763881				
Codominant				
AA	130 (34.3)	142 (31.0)	1	
AC	195 (51.5)	226 (49.2)	1.05 (0.75–1.46)	0.794
CC	54 (14.2)	91 (19.8)	1.50 (0.96–2.34)	0.077
Dominant				
AA	130 (34.3)	142 (31.0)	1	
AC+CC	249 (65.7)	317 (69.0)	1.14 (0.84–1.57)	0.404
Recessive				
AA+AC	325 (85.8)	368 (80.2)	1	
CC	54 (14.2)	91 (19.8)	1.46 (0.98–2.17)	0.064
Additive				
AA	130 (70.7)	142 (60.9)	1	
CC	54 (29.3)	91 (39.1)	1.51 (0.97–2.37)	0.071
Alleles				
A	455 (60)	510 (55.6)	1	
C	303 (40)	408 (44.4)	1.18 (0.96–1.46)	0.119
HWE	0.373	0.998		

Note: ^aAdjusted for age and gender.

Abbreviations: CON, control; GC, gastric cancer; AOR, adjusted odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

Stratified Analysis for rs7763881 SNP

Further, we performed stratified analyses to evaluate the possible association between rs7763881 SNP and GC risk based on various disease characteristics, including age, gender, tumor differentiation, histological type, LNM, T classification, and tumor stage. The results are shown in Table 3. After adjusting age and gender, the rs7763881 recessive model (CC) showed a significant association with an increased GC risk in the undifferentiated (OR = 1.85, 95% CI = 1.17–2.94, $P = 0.009$), diffuse-type GC (OR = 1.72, 95% CI = 1.05–2.82, $P = 0.033$), LNM-positive (OR = 2.02, 95% CI = 1.24–3.27, $P = 0.004$), T3/T4 (OR = 1.75, 95% CI = 1.05–2.91, $P = 0.032$), and tumor stage III (OR = 2.01, 95% CI = 1.17–3.45, $P = 0.011$) subgroups, when compared to the rs7763881 combined genotypes (AA+AC). Furthermore, the rs7763881 additive model (CC) indicated a significantly higher GC risk than rs7763881 AA genotype in the undifferentiated (OR = 1.96, 95% CI = 1.15–3.32, $P = 0.013$), diffuse-type GC (OR = 2.08, 95% CI = 1.23–3.52, $P = 0.004$), and LNM-positive (OR = 2.00, 95% CI = 1.14–3.49, $P = 0.016$) subgroups (Table 3).

Table 3 Stratified Analysis for *HULC* rs7763881 Polymorphism in GC Patients and Controls

Variables	Recessive (CC/AA+AC)				Additive (CC/AA)			
	GC	CON	OR (95% CI) ^a	P ^a	GC	CON	OR (95% CI) [*]	P ^a
Age (years)								
<60	44/154	29/166	1.43 (0.79–2.60)	0.235	44/58	29/73	1.70 (0.86–3.34)	0.125
≥60	47/215	25/159	1.40 (0.79–2.48)	0.243	47/84	25/57	1.27 (0.68–2.39)	0.449
Sex								
Male	67/255	17/104	1.60 (0.89–2.85)	1.114	67/97	17/42	1.70 (0.89–3.24)	1.06
Female	24/113	37/221	1.36 (0.76–2.41)	0.300	24/45	37/88	1.39 (0.72–2.66)	0.327
Tumor Differentiation								
Differentiated	54/325	24/325	1.13 (0.67–1.91)	0.636	36/76	24/130	1.11 (0.62–1.98)	0.736
Undifferentiated	36/186	24/325	1.85 (1.17–2.94)	0.009	47/56	24/130	1.96 (1.15–3.32)	0.013
Histological Type								
Intestinal	43/215	24/325	1.19 (0.73–1.95)	0.494	43/89	24/130	1.13 (0.65–1.95)	0.669
Diffuse	35/113	24/325	1.72 (1.05–2.82)	0.033	35/38	24/130	2.08 (1.23–3.52)	0.004
Lymph Node Metastasis								
Negative	47/239	24/325	1.22 (0.76–1.44)	0.410	47/91	24/130	1.28 (0.77–2.16)	0.344
Positive	44/129	24/325	2.02 (1.24–3.27)	0.004	44/51	24/130	2.00 (1.14–3.49)	0.016
T Classification								
T1/T2	56/245	24/325	1.41 (0.90–2.21)	0.135	56/89	24/130	1.62 (0.97–2.71)	0.065
T3/T4	35/123	24/325	1.75 (1.05–2.91)	0.032	35/53	24/130	1.53 (0.87–2.70)	0.144
Tumor Stage								
I (A+B)/II (A+B+C)	61/269	24/325	1.36 (0.87–2.10)	0.174	61/98	24/130	1.53 (0.93–2.52)	0.093
III (A+B+C)	30/94	24/325	2.01 (1.17–3.45)	0.011	30/44	24/130	1.69 (0.93–3.09)	0.086

Notes: ^aAdjusted by age and gender. The significant results are in bold.

Abbreviations: GC, gastric cancer; CON, controls; OR, odds ratio; CI, confidence interval.

Discussion

In recent years, a number of studies have reported the association of lncRNA *HULC* polymorphisms with decreased risk of HCC, ESCC, and CRC.^{24–27} In this case-control study, we first investigated the association between *HULC* rs7763881 SNP and GC risk but did not observe a significant association between them. However, stratified analysis by age, gender, tumor differentiation, histological type, LNM, T classification, and tumor stage revealed statistically significant association between *HULC* rs7763881 CC genotype and increased GC risk of the undifferentiated, diffuse-type, LNM-positive, T3/T4, and tumor stage III groups. Till date, contradictory to our results, previous studies have reported the relationship between rs7763881 AC or AC+CC genotype with the decreased risk of several cancers, including HBV carried HCC, ESCC, and CRC.^{24–27} Through stratification analysis. Of Chinese populations, Kang et al showed that rs7763881 AC genotype is significantly associated with decreased ESCC risk in male patients compared to

rs7763881 AA genotype. Moreover, stratification analysis of Egyptian populations by Shaker et al suggested that rs7763881 AC genotype is significantly associated with decreased CRC risk in younger patients compared to rs7763881 AA genotype.^{25,27} However, we did not observe the association of rs7763881 genotypes with GC risk in stratified subgroups by age and gender. To evaluate the possible clinical applications of lncRNA as a GC diagnosis biomarker, recent studies have assessed the correlation between lncRNA expression levels and clinical features such as tumor differentiation, histological type, LNM, T classification, and tumor stage in GC and reported their association. Moreover, it has recently been reported that lncRNAs play a pivotal role in development and progression of human cancer. In GC, overexpression of lncRNAs is correlated with clinical features of GC patients such as tumor differentiation, LNM, and tumor stage. Li et al showed an association between enhanced expression of H19 and LN number (N2-3) and tumor stage (III–IV) of GC.⁵ Zhang et al and Liu et al reported the relationship

between HOTAIR overexpression and poor differentiation, LNM, and advanced tumor stage (III–IV).^{8,29} Sun et al showed an association between decreased expression of MEG3 and GAS5 and TNM stage and LNM of GC.^{15,17} Zhao et al revealed the relationship between increased expression of HULC and LNM present and GC tumor stage (III–IV).¹⁹ Ding et al observed a positive correlation between increased expression of PVT1 and LNM of GC.³⁰ Additionally, Hong et al showed an association between lncRNA *PRNCRI* SNPs and risk of GC in LNM-positive and tumor stage III subgroups.³¹ In our data, although we did not investigate the correlation between *HULC* rs7763881 CC genotype and *HULC* gene expression, we found that *HULC* rs7763881 CC genotype in the dominant and additive genetic model was associated with a higher risk for GC of undifferentiated, diffuse-type, LNM-positive, T3/T4, and tumor stage III groups.

There were a few limitations of this case-control study. First, the sample size is relatively small for a stratified analysis, leading to the reduction of the statistical power. Second, we failed to investigate the association between the genetic factors and other clinical features such as *Helicobacter pylori* infection, smoking, drinking, and diet, owing to lack of these data from the GC and control groups. Fourth, large prospective studies are needed to validate our results in different ethnic groups.

Conclusions

In conclusion, based on previous studies and our results, we suggest that *HULC* rs7763881 CC genotype may contribute to GC development by affecting *HULC* as an oncogene. Further studies are required to validate our findings in large populations and different ethnic groups to clarify whether *HULC* rs7763881 CC increases GC risk by altering *HULC* gene expression.

Abbreviations

AOR, adjusted odds ratio; CI, confidence interval; CON, control; CCAT2, colon cancer-associated transcript 2; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GAS5, growth arrest-specific 5; GC, Gastric cancer; H19, imprinted maternally expressed transcript; HCC, hepatocellular carcinoma; HOTAIR, HOX transcript antisense RNA; HULC, highly upregulated in liver cancer; HWE, Hardy Weinberg equilibrium; lncRNAs, long non-coding RNAs; LNM, lymph node metastasis; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MEG 3, maternally expressed 3;

PVT1, Pvt1 oncogene; SD, standard deviation; SNPs, single-nucleotide polymorphisms.

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Disclosure

The authors have declared that no competing interest exists in this work.

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