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ORIGINAL ARTICLE

The analysis of lncRNA *HOTAIR* rs12826786 C>T polymorphism and gastric cancer susceptibility in a Turkish population: lack of any association in a hospital-based case–control study

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Abstract
Background The *HOX transcript antisense intergenic RNA* (*HOTAIR*), a well-known long noncoding RNA (lncRNA), has been widely identified to participate in pathogenesis of multiple cancers. An aberrant up-regulation and biological functions have been observed in gastric cancer (GC). A common single nucleotide polymorphism (SNP) (rs12826786 C>T) at the *HOTAIR* has been reported to influence HOTAIR expression, but its association with GC has yet to be investigated in Turkish population.
Aim The aim of the present study was to investigate whether *HOTAIR* rs12826786 C>T polymorphism could be involved in the risk of GC susceptibility in Turkish population.
Methods We genotyped *HOTAIR* rs12826786 C>T polymorphism in 312 Turkish individuals including 105 GC patients and 207 healthy controls matched on age and gender by a Real-Time Polymerase Chain Reaction (PCR) with the TaqMan assay.
Results No statistically significant differences were found in the allele or genotype distributions of the *HOTAIR* rs12826786 C>T polymorphism among GC and healthy control subjects ($P > 0.05$).
Conclusions Our results demonstrate that the *HOTAIR* rs12826786 C>T polymorphism has not been in any major role in genetic susceptibility to gastric carcinogenesis, at least in the population studied here. Independent studies are needed to validate our findings in a larger series, as well as in patients of different ethnic origins.

Keywords Gastric cancer · Genetic susceptibility · HOTAIR · HOTAIR rs12826786 C>T polymorphism · lncRNA

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Introduction

Gastric cancer (GC) is the fifth most prevalent cancer in the worldwide and the third leading cause of cancer-related deaths [1]. Although, the GLOBOCAN project has showed that a slight decrease in GC incidence and mortality, new diagnosed cases and the deaths are still a relatively large number in Turkey, where particularly GC is the second fatal cause, after lung cancer [1]. However, little is known about the completely mechanism of GC development and progress, despite that obtaining evidences indicate the significant relation between GC etiology and environmental and epigenetic/genetic factors [2]. Single nucleotide polymorphisms (SNPs) are the most common class of genetic susceptibility factors on gastric carcinogenesis [3]. So, determination of functional SNPs may result in the increased estimate of GC susceptibility and provide the earlier application of clinical strategies to decrease mortality percentage of GC [4].

Long noncoding RNAs (lncRNAs) are crucial class of RNAs involved in multiple biologic processes including chromatin remodeling, genome packaging, genome rearrangement, dosage compensation, gene imprinting and regulation of gene expression [5–8]. As one of these RNAs, *Hox transcript antisense intergenic RNA* (*HOTAIR*) is a 2158-nuleotide long lncRNA located on chromosome 12q13.12 and transcribed from the antisense strand of the homebox C (HOXC) genes cluster [9]. Studies have revealed that the major role of *HOTAIR* involves epigenetic regulation of transcription in 40 kb region of HOXD by modifying chromatin structure [9–11]. HOTAIR 5′-domain can recruits the Polycomb Repressive Complex 2 (PRC2), leading to histone H3 lysine 27 trimethylation (H3K27me3) in the HOXD locus, and HOTAIR 3′-domain connects to the LSD1/CoREST/REST complex with H3 lysine 4 demethylation, coordinately regulating the metastasis suppressor genes silence [8]. Clinical and biochemical studies indicated that aberrant overexpression of HOTAIR is a powerful indicator of poor prognosis and malignant progression for several cancers including GC [12–14].

Even with the potential importance of *HOTAIR* in carcinogenesis, little studies have investigated the effects of *HOTAIR* genetic variations (majorly composed of SNPs) on cancer susceptibility [15–21]. Zhang et al. [15] examined the association between three haplotype tagging SNPs (htSNPs) (rs920778 C>T, rs1899663 G>T, rs4759314 A>T) of *HOTAIR* and the risk of esophageal squamous cell carcinoma (ESCC). Among three htSNPs they found that the only *HOTAIR* rs920778 TT genotype increased the risk of ESCC in Chinese population. Furthermore, Pan et al. [16] investigated same htSNPs (rs920778 C>T, rs1899663 G>T, rs4759314 A>T) across the whole *HOTAIR* locus and GC risk. Among *HOTAIR* rs920778 C>T, rs1899663 G>T and rs4759314 A>T polymorphisms they showed that just *HOTAIR* rs920778 TT carriers had increased GC risk in Chinese population [16]. In contrast to these findings, our previous studies have reported opposite results in Turkish population [17, 18]. For instance, we observed CC genotype of *HOTAIR* rs920778 C>T polymorphism increased breast cancer (BC) risk and associated with advanced TNM stage, larger tumor size, distant metastasis and poor histological grade [17]. Interestingly, in another our previous study, we reported that *HOTAIR* rs920778 C>T polymorphism has not been in any major role in susceptibility to GC in Turkish population [18].

Results of studies with other htSNPs (rs4759314 A>G, rs7958904 G>C, rs874945 G>A) of *HOTAIR* are as follows. Xue et al. [19] evaluated the association between *HOTAIR* htSNPs (rs4759314 A>G, rs7958904 G>C, rs874945 G>A) and colorectal cancer (CRC) risk, and they reported that only *HOTAIR* rs7958904 CC genotype decreased CRC risk in Chinese population among three htSNPs. Moreover, Du et al. [20] explored the htSNPs (rs4759314 A>G, rs7958904 G>C, rs874945 G>A) across the whole *HOTAIR* locus and GC risk, and they explained that solely *HOTAIR* rs4759314 G allele carriers had increased GC risk in Chinese population among three htSNPs.

Recently, Guo et al. [21] performed a case–control study in a population of North China to evaluate the possible association between another htSNPs (rs12826786 C>T, rs4759314 A>G, rs10783618 C>T) of *HOTAIR* gene and gastric cardia adenocarcinoma (GCA). Among three htSNPs only the T allele of rs12826786 C>T polymorphism was found to increase the risk of susceptibility GCA. Moreover, subjects with the *HOTAIR* rs12826786 TT genotype showed that a statistical significant higher level of HOTAIR than those with the *HOTAIR* rs12826786 CC genotype in normal tissues and GCA tumor tissues. Similar results were observed between *HOTAIR* rs12826786 TT genotype and *HOTAIR* rs12826786 TC genotype [21].

According to our recent knowledge, no research has been conducted to evaluate the *HOTAIR* rs12826786 C>T polymorphism and risk of GC in a Turkish population. To test the hypothesis that the *HOTAIR* rs12826786 C>T polymorphism is associated with the risk of developing GC in Turkish population, we performed genotyping analysis using TaqMan Real-Time Polymerase Chain Reaction (PCR) assay in a hospital-based case–control study of 105 GC patients and 207 age and gender-matched healthy controls.

Methods

Study population

The present hospital-based case–control study was performed on 105 GC cases, and a total of 207 age and sex matched healthy controls collected between October 2013 and October 2015. Fasting venous blood was collected and all enrolled participants were diagnosed based on their histopathological examinations.

Medical histories were obtained by questionnaire which structured to acquire information on demographic factors and the records were computerized. Detailed participant characteristics are summarized in Table 1.

DNA extraction

Whole blood samples were collected into a test tube containing EDTA from GC patients and healthy controls. None of the GC patients received chemotherapy or radiotherapy prior to whole blood collection. Genomic DNA was

Table 1 Clinical characteristics of GC cases and controls enrolled in current study

Characteristic	Gastric cancer ($n = 105$)	Controls ($n = 207$)	P
Age (year, mean ± SD)	57.56 ± 13.68	57.74 ± 13.96	0.92
Gender			0.56
Males	67 (63.8%)	125 (60.4%)	
Females	38 (36.2%)	82 (39.6%)	
Smoking status			0.93
Smokers	55 (52.4%)	108 (52.2%)	
Non-smokers	50 (47.6%)	99 (47.8%)	
Drinking status			0.28
Drinker	6 (5.7%)	29 (14.0%)	
Non-drinker	99 (94.3%)	180 (86.0%)	
Helicobacter pylori			
Positive	47 (44.8%)		
Negative	58 (55.2%)		
Tumor location			
Non-cardia	90 (85.7%)		
Cardia	15 (14.3%)		
Tumor size			
≤5 cm	73 (69.5%)		
>5 cm	32 (30.5%)		
Distant metastasis			
M0	74 (71.4%)		
M1	31 (28.6%)		
Family history of cancer			
Yes	12 (11.4%)		
No	93 (88.6%)		

isolated from the whole blood specimen of all participants using the AxyPrep Blood Genomic DNA Miniprep KitAP-MN-BL-GDNA-250 (Wujiang, Jiangsu, China) according to the manufacturer's directions. The quantity and quality of DNA was identified by the Qubit® Fluorometer (Invitrogen, Carlsbad, CA, USA).

Genotyping

Genotyping was done by TaqMan SNP Genotyping Assay (Assay ID numbers for rs12826786: C__31185830_10, Life Sciences) according to the protocols described by the manufacturers (Applied Biosystems, Foster City, CA, USA). TaqMan Real-Time PCR was performed in 10 μL reaction mix including 10 ng genomic DNA. TaqMan PCR was conducted with the LightCycler 96 instrument (Roche Diagnostics). The following cycling conditions were used: initial denaturation at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s, and 60 °C for 1 min. *HOTAIR* rs12826786 C>T polymorphism was genotyped with success rate of 100%. The genotyping results were determined LightCycler Genotyping software (Roche Diagnostics). To ensure quality control, genotyping was performed without knowledge of the subjects' case/control status and a 15% random sample of cases and controls was genotyped twice by different persons; reproducibility was 100%.

Statistical analysis

Effective sample sizes for case–control study, and to obtain 80% power was calculated by Quanto (version 1.1.) software (http://hydra.usc.edu/gxe) using minor allele frequency data from HapMap (http://hapmap.ncbi.nlm.nih.gov/) [22]. Data analysis was performed using the computer software Statistical Package for Social Sciences (SPSS; SPSS, Inc., Chicago, IL, USA) for Windows (version 16.0). Descriptive statistics of GC patients and healthy controls in this study were presented as the mean (standard deviation, SD) for continuous variables, while frequencies (%) were used for categorical variables. Comparisons in the distributions of demographical characteristics between the patients with GC and healthy control subjects were evaluated using the Student's t test and Chi-square (χ^2) test. The observed genotype frequencies were compared with expected values calculated from Hardy–Weinberg equilibrium theory using a χ^2 test with degree of freedom equal

to 1 in the control subjects (http://www.oege.org/software/hwe-mr-calc.shtml) [23]. Statistical analysis of genotypes was analyzed using the website for SNP Statistics: http://bioinfo.iconcologia.net/snpstats/start.htm [24]. Logistic regression analysis was used to analyses the association of genotypes in inheritance models (codominant, dominant, recessive, overdominant and log-additive) in the case and control groups. Results are expressed as odds ratios with 95% confidence interval (CI). All tests were two-sided and P value <0.05 was considered significant.

Results

A total of 312 age and gender matched Turkish subjects (105 GC patients and 207 healthy controls) were genotyped to explore the possible relation between *HOTAIR* rs12826786 C>T polymorphism and GC susceptibility in this study. Clinical characteristics of GC patients and healthy controls are demonstrated in Table 1. As expected, the mean age of GC patients and healthy controls paired properly ($P = 0.92$). In addition, no statistically significant difference was found between two groups according to gender which implied that gender matched equally ($P = 0.56$). Moreover, there were no statistically significant differences in smoking status and alcohol consumption among two groups. In addition to these, Table 1 shows the distribution of clinical features such as *H. pylori* infection, tumor location, tumor size, distant metastasis, and family history of cancer.

The frequency distributions of the *HOTAIR* rs12826786 C>T polymorphism genotypes and alleles in GC patients and in healthy controls are shown in Table 2. The genotype frequency distributions of the *HOTAIR* rs12826786 C>T polymorphism did not depart from the in Hardy–Weinberg equilibrium in the healthy controls ($P = 0.94$). The allelic frequencies of GC patients (C, 0.59; T, 0.41) were not statistically significantly different from those of the healthy controls (C, 0.59; T, 0.41) ($P = 0.88$). Thus, genotypic frequencies of the *HOTAIR* rs12826786 C>T polymorphism in the GC patients were similar to that of the healthy controls ($\chi^2 = 0.34$, $df = 2$, $P = 0.85$).

To define whether there was a statistically significant increased risk of GC susceptibility in terms of the *HOTAIR* rs12826786 C>T genotypes, we carried out logistic regression analysis. As shown in Table 2, no significant association between *HOTAIR* rs12826786 C>T polymorphism and the risk of GC susceptibility was determined in any genetic model and allele contrast (C vs. T: OR = 1.03, 95% CI 0.73–1.44, $P = 0.$ 0.88; CC vs. CT: OR = 0.91, 95% CI 0.54–1.54, $P = 0.73$; CC vs. TT: OR = 1.10, 95% CI 0.56–2.16, $P = 0.79$; CC vs. CT+TT: OR = 0.96, 95% CI 0.59–1.57, $P = 0.87$; CC+CT vs. TT: OR = 1.16, 95% CI 0.63–2.12, $P = 0.64$; CC+TC vs. CT: OR = 0.88, 95% CI 0.55–1.42, $P = 0.61$).

Finally, we performed a stratification analysis which revealed no statistically significant relations between the *HOTAIR* rs12826786 C>T genotypes and GC susceptibility by subgroups of age, gender, *H. pylori* infection, tumor location, tumor size, distant metastasis and family history of cancer (Table 3).

Discussion

Deeper understanding of lncRNAs and their role in carcinogenesis could possess a large number of potential clues for developing novel therapeutic agents for GC. HOTAIR, as a functional lncRNA expressed from the developmental HOXC locus, has been widely reported to participate in multiple cancers [5–14]. Recently, emerging evidence has shown that genetic variants in *HOTAIR* may modulate individual susceptibility to cancer [15–21], and exerts effects on HOTAIR expressions and functions [15, 21]. This molecular epidemiological study examined whether the functional *HOTAIR* rs12826786 C>T could have an effect on susceptibility to GC. To the best of our knowledge, this is the first epidemiological study addressing the association between *HOTAIR* rs12826786 C>T polymorphism and gastric carcinogenesis susceptibility in a Turkish population.

Contrary to our expectation, distribution of *HOTAIR* rs12826786 C>T genotype was not different between GC cases and healthy controls in the present hospital-based case–control study. In addition, no statistically significant association emerged between risk of GC and *HOTAIR* rs12826786 C>T polymorphism in overall statistical analyses. The findings of our study are different from to those reported by Guo et al. [21], who showed that the T allele of *HOTAIR* rs12826786 C>T polymorphism was associated with higher risk of developing GCA in population of north China. The *HOTAIR* rs12826786 C>T polymorphism locates in the promoter region of HOTAIR, and a significant higher level of HOTAIR was observed in subjects carrying *HOTAIR* rs12826786 TT genotype than those with CC genotype in normal and GCA tumor tissues, indicating C to T transition may influence the HOTAIR transcription and finally influence the expression of the gene [21]. The significant difference in the results compared to the findings in north China population may be attributable to the limited sample size in our hospital-based case–control study, obvious genetic background difference between Chinese and Turkish population, and dissimilarities of genotyping techniques as well as random errors. For example, population differences have been observed concerning the allele frequency of several polymorphisms

Table 2 Alleles/genotypes frequency and models inheritance for *HOTAIR* rs12826786 C>T polymorphism GC patients and control subjects as well as the association with risk of GC

	Gastric cancer $n = 105$ (%)	Controls $n = 207$ (%)	OR (95% CI)	*P* value[a]	AIC[b]	BIC[c]
Allele						
C	123 (59.0%)	245 (59.0%)	1.00 (reference)			
T	87 (41.0%)	169 (41.0%)	1.03 (0.73–1.44)	0.88		
Codominant						
CC	38 (36.2%)	73 (35.3%)	1.00 (reference)		404.2	415.4
CT	47 (44.8%)	99 (47.8%)	0.91 (0.54–1.54)	0.73		
TT	20 (19.0%)	35 (16.9%)	1.10 (0.56–2.16)	0.79		
Dominant						
CC	38 (36.2%)	73 (35.3%)	1.00 (reference)		402.5	410.0
CT+TT	67 (63.8%)	134 (64.7%)	0.96 (0.59–1.57)	0.87		
Recessive						
CC+CT	85 (81.0%)	172 (83.1%)	1.00 (reference)		402.3	409.8
TT	20 (19.0%)	35 (16.9%)	1.16 (0.63–2.12)	0.64		
Overdominant						
CC+TT	58 (55.2%)	108 (52.2%)	1.00 (reference)		402.3	409.8
CT	47 (44.8%)	99 (47.8%)	0.88 (0.55–1.42)	0.61		
Log-additive	–	–	1.02 (0.74–1.43)	0.89	402.5	410.0

[a] Data were calculated by logistic regression analysis

[b] *AIC* Akaike's information criterion

[c] *BIC* Bayesian information criterion

(International HapMap Project). Based on the HapMap Project data (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=12826786), allele frequency of *HOTAIR* rs12826786 C>T polymorphism display differences among different ethnic populations (Table 4).

A few possible limitations of this hospital-based case–control study are as follows. (1) Because it was a hospital-based case–control study and a large majority of GC cases and healthy controls were from Adıyaman state hospital, inherent choice bias might be present. Therefore, it is crucial to verify results of our hospital-based case–control study in population-based prospective study in the future. (2) The statistical strength of this study may be limited by the sample size, particularly for statistical analyses of subgroups which are stratified by age, sex, *H. pylori* infection, tumor location, tumor size, distant metastasis, and family history of cancer. For this reason, prospective case–control studies with larger sample size should be performed to verify the association between *HOTAIR* rs12826786 C>T polymorphism and GC risk. (3) This hospital-based case–control study is also restricted by the Turkish ethnicity because discrepancies in allele frequency have been ascertained for *HOTAIR* rs12826786 C>T polymorphism in the different populations (Table 4). Further studies on different populations are needed to verify our findings and to reach convincing results on evaluating the association between *HOTAIR* rs12826786 C>T polymorphism and GC susceptibility risk. (4) This study only focused on single locus on single gene without taking into consideration gene-environment, gene–gene interactions and interactions between different locuses on the same gene, which may affect individual susceptibility to GC. Because of advances in high-throughput genotyping techniques, it is likely that future association studies on GC will need to investigate multiple polymorphisms within *HOTAIR* gene and will need to use recently developed haplotype-based methods to evaluate the haplotypic effects. (5) Due to the lack of data on HOTAIR expression according to *HOTAIR* rs12826786 C>T genotypes in our GC group, future work need to be done to explore the correlation between levels of HOTAIR both normal and GC tissues in the context of different genotypes of *HOTAIR* rs12826786 C>T polymorphism.

In conclusion, our findings suggest that the *HOTAIR* rs12826786 C>T polymorphism has not played any major role in genetic susceptibility to gastric carcinogenesis within the Turkish population. Further independent studies are required to validate our findings in a larger series, as well as in patients of different ethnic origins, and to better

Table 3 Comparison of characteristics of GC patients according to the *HOTAIR* rs12826786 C>T polymorphism genotypes

Valuables	*HOTAIR* rs12826786 C>T polymorphism			*P*
	CC	CT	TT	
Age ± SD	56.82 ± 14.58	57.49 ± 14.60	58.95 ± 11.87	0.86
Sex				0.60
Male	22 (32.8%)	31 (46.3%)	14 (20.9%)	
Female	16 (42.1%)	16 (42.1%)	6 (15.8%)	
Smoking status				0.14
Smokers	18 (33.3%)	22 (39.6%)	15 (27.1%)	
Non-smokers	17 (34.1%)	27 (54.5%)	6 (11.4%)	
Drinking status				0.52
Drinker	2 (40.0%)	4 (60.0%)	0 (0%)	
Non-drinker	33 (33.3%)	46 (46.0%)	20 (20.7%)	
Helicobacter pylori				0.31
Positive	10 (22.3%)	21 (44.4%)	16 (33.3%)	
Negative	26 (45.5%)	19 (31.8%)	13 (22.7%)	
Tumor location				0.60
Non-cardia	30 (33.8%)	41 (45.5%)	19 (20.7%)	
Cardia	7 (46.2%)	5 (30.8%)	3 (23.0%)	
Tumor size				0.11
≤5 cm	22 (30.0%)	32 (43.3%)	19 (26.7%)	
>5 cm	14 (46.2%)	14 (46.2%)	3 (7.6%)	
Distant metastasis				0.09
M0	23 (31.6%)	30 (40.4%)	21 (28.0%)	
M1	9 (29.2%)	19 (62.5%)	3 (8.3%)	
Family history of cancer				0.66
Yes	5 (40.0%)	6 (50.0%)	1 (10.0%)	
No	31 (33.8%)	41 (43.8%)	21 (22.5%)	

Table 4 Allele frequencies of *HOTAIR* rs12826786 C>T polymorphism according to the HapMap Data

Population ID	Individual Group	C allele frequency of HOTAIR rs12826786 polymorphism	T allele frequency of HOTAIR rs12826786 polymorphism
HapMap-JPT	Asian (Japanese)	0.887	0.112
HapMap-HCB	Asian (Han Chinese)	0.837	0.163
Gu et al. (2015)	Chinese (Han Chinese)	0.793	0.207
HapMap-CEU	European	0.684	0.316
Present study	Turkish	0.591	0.409
HapMap-YRI	Sub-Saharan African (Nigeria)	0.527	0.473

understand *HOTAIR* rs12826786 C>T polymorphism and susceptibility to GC.

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Compliance with ethical standards

Conflict of interest All of the authors declare that there are no conflicts of interest.

Ethical approval This study was approved by the Human Ethics Committee of Firat University (Elazığ, Turkey). Submission of the individuals to the study was conditioned by an obtained written informed consent form regarding the use of their blood samples for research studies. The study proceeded in agreement with the Helsinki declaration approved by the World Medical Association meeting in Edinburgh.

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Informed consent Informed consent was obtained from all individual participants included in the study.

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