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ORIGINAL ARTICLE

A functional *HOTAIR* rs920778 polymorphism does not contributes to gastric cancer in a Turkish population: a case–control study

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Abstract An aberrant up-regulation of *HOX transcript antisense intergenic RNA* (*HOTAIR*), a long non-coding RNA (lncRNA), is associated with human cancers including gastric cancer (GC) and worse clinicopathological features. A naturally occurring functional single nucleotide polymorphism (SNP) rs920,778 (C→T) in the intronic enhancer of *HOTAIR* gene has been demonstrated to affect HOTAIR expression and cancer susceptibility. To investigate the association of the *HOTAIR* rs920778 polymorphism on the risk of GC susceptibility in Turkish population, a hospital-based case–control study was carried out consisting of 104 GC and 209 healthy control subjects matched on age and gender. The genotype frequency of *HOTAIR rs920778* polymorphism was determined by using TaqMan Real-Time Polymerase Chain Reaction. No statistically significant differences were found in the allele or genotype distributions of the *HOTAIR* rs920778 polymorphism among GC and healthy control subjects ($P > 0.05$). Our results demonstrate that the *HOTAIR* rs920778 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 · *HOTAIR* · lncRNA · *HOTAIR* rs920778 polymorphism · Genetic susceptibility

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Introduction

Gastric cancer (GC) is the fifth most common type of human malignancies in the world and the mortality of GC is the third leading cause of cancer related deaths in both gender with an estimated 952,000 new cases and 723,000 deaths in 2012 [1, 2]. In Turkey, GC is the sixth most common cancer and is ranked the second leading cause of cancer related deaths [2]. It is now well established that multiple risk factors contribute to gastric carcinogenesis, including environmental and genetic factors [3]. Among the environmental factors *Helicobacter pylori* infection is the best known [3]. Although *H. pylori* infection has been shown to exist in 40–80 % of people, just <3 % of infected people develop GC throughout their lifetime, supporting a crucial role for a genetic factor in gastric carcinogenesis [3]. Single nucleotide polymorphisms (SNPs) are the most common class of genetic susceptibility factors for gastric carcinogenesis [4]. Therefore, identification of functional SNPs may result in the enhanced estimate of GC

susceptibility and ensure the earlier application of clinical strategies to reduce mortality percentage of GC [5].

Hox transcript antisense intergenic RNA (*HOTAIR*) is a well-studied long non-coding RNA (lncRNA) with 2158 nucleotides in length which is expressed from the antisense strand of the HOXC gene [6]. Several studies display an active role of aberrant up regulation of *HOTAIR* in human cancers including GC [7–13]. In all studies, elevated expression of *HOTAIR* in both primary and metastasized tumors is associated with malignant progression and poor survival, suggesting *HOTAIR* exerts its effect through altering the expression of some genes involved in cancer progression [13, 14]. Additionally, Zhang et al. [8] recently summarized the data from nineteen *HOTAIR* studies using a quantitative meta-analysis approach. Authors found that HOTAIR expression may serve as a novel predictive factor for poor prognosis in human cancers. For instance, HOTAIR expression was found to be significantly associated with lymph node metastases and vessel invasion without obvious heterogeneity in GC. All these convincing proofs indicate the oncogenic role of HOTAIR in the course of several forms of human carcinogenesis including GC. Hence, *HOTAIR* may be considered as a potential target for diagnosis and treatment of various cancer types.

A Homo sapiens *HOTAIR* gene was mapped to chromosome 12q13.13 and contains many SNPs (http://www.ncbi.nlm.nih.gov/snp/?term=hotair). Recently, a SNP has been identified in the intron 2 of *HOTAIR* gene [cytosine to thymine (C→T)] (rs920778). Moreover, Zhang et al. [15] identified a novel intronic *HOTAIR* enhancer located on intron 2 of *HOTAIR* gene. The results from that study showed that *HOTAIR* rs920778 located within this enhancer region has a genotype specific effect on HOTAIR expression [15]. Molecular epidemiological studies have investigated the association between the *HOTAIR* rs920778 polymorphism and the cancer risk including esophageal squamous cell carcinoma (ESCC), breast cancer (BC) and GC [15–17]. However, the results of these studies have remained controversial [15–17]. For example, Zhang et al. [15] reported that TT genotype of *HOTAIR* rs920778 polymorphism had increased ESCC risk in Chinese Jinan, Shijiazhuang and, Huaian populations. In addition to this, Pan et al. [17] found that *HOTAIR* rs920778 TT carriers had a 1.66 and 1.87-fold increased GC risk in Chinese Jinan and Huaian populations compared with the CC carriers, respectively. However, Bayram et al. [16] showed that the CC genotype of *HOTAIR* rs920778 polymorphism significantly increased the risk of breast cancer in Turkish population.

In view of the role that *HOTAIR* plays in carcinogenesis and tumor formation, we also hypothesized that functional *HOTAIR* rs920778 polymorphism may act as a genetic susceptibility factor to GC in a Turkish population. According to our recent knowledge, no research has been conducted to evaluate the *HOTAIR* rs920778 polymorphism and risk of GC in a Turkish population. To test the hypothesis that the *HOTAIR* rs920778 polymorphism is associated with the risk of developing GC in a Turkish population, we performed genotyping analysis using TaqMan Real-Time Polymerase Chain Reaction (PCR) assay in a hospital-based case–control study of 104 GC patients and 209 age and gender-matched healthy controls.

Materials and methods

Study population

The present case–control study was performed on 104 GC cases, and a total of 209 age and sex matched healthy controls collected between October 2013 and November 2014. Fasting venous blood was collected and all enrolled participants were diagnosed based on their histopathological examinations.

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

DNA extraction

Five mL sample of venous blood was collected from each subject into a test tube containing EDTA as anticoagulant. Genomic DNA was extracted from peripheral whole blood using High Pure PCR Template Preparation Kit (Roche Diagnostics. GmbH, Mannheim, Germany) according to the manufacturer's protocol.

Genotyping

Genotyping was done by TaqMan SNP Genotyping Assay (Assay ID numbers for rs920778: C___9162435_20, Life Technologies) according to the protocols as described previously [16]. 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*

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

Characteristic	Gastric cancer (n = 104)	Controls (n = 209)	*P*
Age (year, mean ± SD)	57.42 ± 13.77	57.71 ± 13.45	NS
Gender			NS
Males	66 (63.5 %)	125 (59.8 %)	
Females	38 (36.5 %)	84 (40.2 %)	
Smoking status			0.77
Smokers	56 (53.8 %)	109 (52.2 %)	
Non-smokers	48 (46.2 %)	100 (47.8 %)	
Drinking status			0.28
Drinker	10 (9.6 %)	29 (13.9 %)	
Non-drinker	94 (90.4 %)	180 (86.1 %)	
Helicobacter pylori			
Positive	47 (45.2 %)		
Negative	57 (54.8 %)		
Tumor location			
Non-Cardia	88 (84.6 %)		
Cardia	16 (15.4 %)		
Tumor size			
≤5 cm	72 (69.2 %)		
>5 cm	32 (30.8 %)		
Distant metastasis			
M0	73 (70.2 %)		
M1	31 (29.8 %)		
Family history of cancer			
Yes	12 (11.5 %)		
No	92 (88.5 %)		

NS: not significant

rs920778 polymorphism was genotyped with a success rate of 100 %. The genotyping results were determined by 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/) [18]. 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 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 control subjects were evaluated using the Student's *t* test and Chi square ($\chi 2$) test. The observed genotype frequencies were compared with expected values calculated from Hardy–Weinberg equilibrium theory by using a $\chi 2$ test with degree of freedom equal to 1 in the control subjects (http://www.oege.org/software/hwe-mr-calc.shtml) [19]. Statistical analysis of genotypes was analyzed using the website for SNP Statistics: http://bioinfo.iconcologia.net/snpstats/start.htm [20]. Logistic regression analysis was used to analyze 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 313 age and gender matched Turkish subjects (104 GC patients and 209 healthy controls) were genotyped to explore the possible relation between *HOTAIR* rs920778

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 ($P = 0.86$). In addition, no statistically significant difference was found between the two groups according to gender which implied that gender matched equally ($P = 0.53$). Moreover, there were no statistically significant differences in smoking status and alcohol consumption between the 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* rs920778 polymorphism genotypes and alleles in GC patients and in healthy controls are shown in Table 2. The genotype frequency distributions of the *HOTAIR* rs920778 polymorphism did not depart from the Hardy–Weinberg equilibrium in the healthy controls ($P = 0.95$). The allelic frequencies of GC patients (T 0.56; C 0.44) were not statistically significantly different from those of the healthy controls (T 0.57; C 0.43) ($P = 0.83$). Thus, genotypic frequencies of the *HOTAIR* rs920778 polymorphism in the GC patients were similar to those of the healthy controls ($\chi 2 = 0.06$, $df = 2$, $P = 0.97$).

To define whether there was a statistically significant increased risk of GC susceptibility in terms of the *HOTAIR* rs920778 genotypes, we carried out logistic regression analysis. As shown in Table 2, no significant association between *HOTAIR* rs920778 polymorphism and the risk of GC susceptibility was determined in any genetic model and allele contrast (T vs. C: OR 1.04, 95 % CI 0.74–1.45, $P = 0.83$; TT vs. TC: OR 1.00, 95 % CI 0.58–1.72, $P = 0.98$; TT vs. CC: OR 1.06, 95 % CI 0.53–2.12, $P = 0.82$; TT vs. TC + CC: OR 1.02, 95 % CI 0.61–1.70, $P = 0.95$; TT + TC vs. CC: OR 1.06, 95 % CI 0.58–1.94, $P = 0.85$; TT + CC vs. TC: OR 0.98, 95 % CI 0.61–1.57, $P = 0.93$).

Finally, we performed a stratification analysis which revealed no statistically significant relations between the *HOTAIR* rs920778 genotypes and gastric cancer susceptibility by subgroups of age, gender, *H. pylori* infection, tumor location, tumor size, distant metastasis and family history of cancer (Table 3).

Discussion

This molecular epidemiological study examined whether the functional *HOTAIR* rs920778 polymorphism 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* rs920778 polymorphism and gastric carcinogenesis susceptibility in a Turkish population. *HOTAIR* was chosen as the candidate gene

Table 2 Alleles/genotypes frequency and models inheritance for *HOTAIR* rs920778 polymorphism among GC patients and control subjects as well as the association with risk of GC

	Gastric cancer n = 104 (%)	Controls n = 209 (%)	OR (95 % CI)	*P* value[a]	AIC[b]	BIC[c]
Allele						
T	116 (55.8 %)	237 (56.7 %)	1.00 (Reference)			
C	92 (44.2 %)	181 (43.3 %)	1.04 (0.74–1.45)	0.83		
Codominant						
TT	32 (30.8 %)	66 (31.6 %)	1.00 (Reference)		405.6	405.6
TC	52 (50.0 %)	105 (50.2 %)	1.00 (0.58–1.72)	0.98		
CC	20 (19.2 %)	38 (18.2 %)	1.06 (0.53–2.12)	0.82		
Dominant						
TT	32 (30.8 %)	66 (31.6 %)	1.00 (Reference)		403.6	414.8
TC + CC	72 (69.2 %)	143 (68.4 %)	1.02 (0.61–1.70)	0.95		
Recessive						
TT + TC	84 (80.8 %)	171 (81.8 %)	1.00 (Reference)		403.6	414.8
CC	20 (19.2 %)	38 (18.2 %)	1.06 (0.58–1.94)	0.85		
Overdominant						
TT + CC	52 (50.0 %)	104 (49.8 %)	1.00 (Reference)		403.6	414.8
TC	52 (50.0 %)	105 (50.2 %)	0.98 (0.61–1.57)	0.93		
Log-additive	–	–	1.03 (0.73–1.44)	0.88	403.6	414.8

[a] Data were calculated by logistic regression analysis

[b] AIC Akaike's information criterion

[c] BIC Bayesian information criterion

Table 3 Comparison of characteristics of GC patients according to the *HOTAIR* rs920778 polymorphism genotypes

Valuables	*HOTAIR* rs920778 polymorphism			*P*
	TT	TC	CC	
Age ± SD	55.16 ± 12.98	58.23 ± 14.95	58.95 ± 11.87	0.53
Sex				0.16
Male	16 (24.3 %)	36 (54.5 %)	14 (21.2 %)	
Female	16 (42.1 %)	16 (42.1 %)	6 (15.8 %)	
Smoking status				0.25
Smokers	17 (30.4 %)	25 (44.6 %)	14 (25.0 %)	
Non-smokers	15 (14.8 %)	27 (24.0 %)	6 (9.2 %)	
Drinking status				0.18
Drinker	5 (50.0 %)	5 (50.0 %)	0 (0 %)	
Non-drinker	27 (28.7 %)	47 (50.0 %)	20 (21.3 %)	
Helicobacter pylori				0.32
Positive	10 (21.3 %)	21 (44.7 %)	16 (34.0 %)	
Negative	16 (28.1 %)	29 (50.9 %)	12 (21.0 %)	
Tumor location				0.90
Non-Cardia	27 (30.7 %)	43 (48.9 %)	18 (20.5 %)	
Cardia	5 (31.2 %)	7 (43.8 %)	4 (25.0 %)	
Tumor size				0.11
≤5 cm	20 (27.8 %)	32 (44.4 %)	20 (27.8 %)	
>5 cm	11 (34.4 %)	18 (56.2 %)	3 (9.4 %)	
Distant metastasis				0.06
M0	21 (28.8 %)	31 (42.4 %)	21 (28.8 %)	
M1	8 (25.8 %)	20 (64.5 %)	3 (9.7 %)	
Family history of cancer				0.51
Yes	4 (33.3 %)	7 (58.3 %)	1 (8.4 %)	
No	27 (29.3 %)	44 (47.8 %)	21 (22.8 %)	

because our knowledge of HOTAIR expression patterns and function in normal or cancerous gastric cells is just starting to increase [11–13] Nevertheless, the exact mechanisms that regulate *HOTAIR* expression are uncertain, and low penetrance genetic impact of *HOTAIR* on cancer susceptibility, diagnosis, and prognosis is still unknown [15]. Contrary to our expectation, distribution of *HOTAIR* rs920778 genotype was not different between GC cases and healthy controls in the present case–control study. Also, no statistically significant association emerged between risk of GC and *HOTAIR* rs920778 polymorphism in overall statistical analyses. However, a reduced distant metastasis risk and smaller tumor size (≤5 cm) was possibly related with C allele of *HOTAIR* rs920778 polymorphism. Relationship between C allele of *HOTAIR* rs920778 polymorphism and clinicopathologic features such as distant metastasis and tumor size was not statistically significant ($P > 0.05$). The findings of our study are different from those reported by Pan et al. [17], who showed that *HOTAIR* rs920778 TT genotype increased GC risk in Chinese Jinan and Huaian populations when compared to CC genotype. In addition to this, Zhang et al. [15] demonstrated that the TT genotype of *HOTAIR* rs920778 polymorphism increased susceptibility to ESCC in a Chinese population. It is feasible that the important difference in the findings of these studies may be owing to differences in the genetic background of studied populations, inconsistencies in sample sizes, varieties of cancers, and dissimilarities of genotyping techniques as well as random errors. For example, population differences have been observed concerning the allele frequency of several polymorphisms (International HapMap Project). Based on the HapMap Project data (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=920778), allele frequency of *HOTAIR* rs920778 polymorphism displays significant differences among different ethnic populations (Table 4). In this study we found that the C allele frequency of *HOTAIR* rs920778 polymorphism was 0.433 in our healthy Turkish control subjects, similar to the defined allele frequencies in Caucasian populations (HapMap-CEU and Bayram et al. [16]) (Table 4). In the study performed by Zhang et al. [15], the frequency of the C allele was determined to be 0.790 in Chinese Jinan, Shijiazhuang, and Huaian populations. In addition to this, Pan et al. [17] reported that C

allele frequency of *HOTAIR* rs920778 polymorphism was 0.792 in Chinese Jinan and Huaian populations. However, C allele frequency of *HOTAIR* rs920778 polymorphism of healthy subjects from Chinese Jinan, Shijiazhuang, and Huaian populations are not similar to HapMap data of Chinese populations (HapMap-CH, HapMap-CHD and HapMap-HCB) (Table 4) [15, 17]. Additionally, in a recently conducted study form Chinese population has shown that genotype and allele frequencies of another *HOTAIR* polymorphism (rs4759314) were different between healthy controls and HapMap data [21]. Even though, healthy controls and subjects of HapMap were from Chinese Han population [21]. Differences from HapMap data may have resulted from the method used for genotyping. The polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) genotyping technique is used in these studies [15, 17, 21]. It should be reported that our previous study has shown that the CC genotype of *HOTAIR* rs920778 polymorphism significantly increased the risk of BC in a Turkish population [16]. Also, *HOTAIR* rs920778 CC genotype was observed related to be clinicopathologic features of BC, including advanced tumor-node-metastasis (TNM) stage, larger tumor size, distant metastasis, and poor histological grade [16]. This cancer-dependent difference in risk conferred by the examined *HOTAIR* rs920778 may be attributable to differences in the pathways of carcinogenesis among the various types of human cancers.

A few possible limitations of this case–control study are as follows. (i) 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 case–control study in population-based prospective study in the future. (ii) 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* rs920778 polymorphism and GC risk. (iii) This hospital-based case–control study is also restricted by the Turkish ethnicity because discrepancies in allele frequency have been ascertained for *HOTAIR* rs920778 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* rs920778 polymorphism and GC susceptibility risk. (iv) In Chinese individuals, Zhang et al. [15] and Pan et al. [17] showed that T allele of *HOTAIR* rs920778 polymorphism causes statistically significant enhanced expression of HOTAIR in normal tissues (gastric and esophagus) but not in cancer tissues (ESCC and GC). Because of the controversial status of the expression of HOTAIR according to *HOTAIR* rs920778 polymorphism in normal and cancer tissues, and lack of results on HOTAIR expression according to *HOTAIR* rs920778 polymorphism in the present study, further study is required to verify *HOTAIR* rs920778 polymorphism influences expression of HOTAIR both normal and cancer gastric tissues.

Table 4 Allele frequencies of *HOTAIR* rs920778 polymorphism according to the HapMap Data

Population ID	Individual Group	C allele frequency of HOTAIR rs920778 polymorphism	T allele frequency of HOTAIR rs920778 polymorphism
HapMap-CHB	Asian (Han Chinese)	0.171	0.829
HapMap-JPT	Asian (Japanese)	0.198	0.802
HapMap-CHD	Chinese in Metropolitan Denver, Colorado.	0.253	0.747
HapMap-TSI	Toscans in Italy	0.290	0.710
HapMap-HCB	Asian (Han Chinese)	0.314	0.686
HapMap-CEU	European	0.336	0.664
Bayram et al. [16]	Turkish (only women)	0.393	0.607
HapMap-GIH	Gujarati Indians in Houston, Texas	0.420	0.580
HapMap-MEX	Mexican ancestry in Los Angeles, California	0.420	0.580
Present study	Turkish (both gender)	0.433	0.567
HapMap-MKK	Maasai in Kinyawa, Kenya.	0.597	0.403
HapMap-ASW	African ancestry in Southwest USA	0.663	0.337
HapMap-YRI	Sub-Saharan African (Nigeria)	0.690	0.310
HapMap-LWK	Luhya in Webuye, Kenya.	0.706	0.294
Pan et al. [17]	Chinese (Jinan and Huaian)	0.792	0.208
Zhang et al. [15]	Chinese (Jinan, Shijiazhuang and Huaian)	0.790	0.210

In conclusion, our findings suggest that the *HOTAIR* rs920778 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 understand *HOTAIR* rs920778 polymorphism and susceptibility to GC.

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

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