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Original Research

Effect of *HOTAIR* rs12826786 and rs1899663 polymorphisms on lung cancer susceptibility and clinicopathological characteristics in a turkish population: a hospital-based case-control study

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Abstract: Overexpression of Hox transcript antisense intergenic RNA (HOTAIR), a long non-coding RNA (lncRNA), is associated with tumorigenesis and multiple cancer types including lung cancer. In this study, the association between two HOTAIR single nucleotide polymorphisms (SNPs) (rs12826786 and rs1899663) on the risk and clinical characteristics of lung cancer in a Turkish population was investigated. We genotyped HOTAIR rs12826786 and rs1899663 polymorphisms in 180 Turkish people including 87 lung cancer patients (71 males and 16 females) and 93 age-matched healthy controls (67 males and 26 females) by a TaqMan real-time polymerase chain reaction method. The mean age value of the lung cancer patients and control subjects were 59.27 ± 10.55 and 61.77 ± 12.00, respectively. We found that none of the two HOTAIR polymorphisms (rs12826786 T>C, rs1899663A>C) has any significant association with the increased risk of lung cancer in any type of inheritance genetic models. However, our research indicated that carriers of Trs12826786/Crs1899663 (ht3) (P = 0.03) had an increased risk of lung cancer susceptibility.

Key words: Genetic susceptibility; HOTAIR; Lung cancer; HOTAIR rs12826786 polymorphism; HOTAIR rs1899663 polymorphism.

Introduction

Lung cancer (LC) is among the most common cancer types and its rate of morbidity and mortality (resulting in more than 1.3 million deaths per year) continue to increase worldwide (1,2). In developing countries including Turkey, the morbidity and mortality rates of LC keep at high numbers due to increase of environmental pollution particularly air pollution, which is caused mainly by the industrial development (3). Metastasis in LC is a very complicated process. As described by Popper, these processes could be divided as angiogenesis, hypoxia, circulation, and establishment of a metastatic focus and several of these processes may overlap and occur simultaneously (4). Mostly, tumors are discovered as locally advanced or metastatic disease. Clinical and experimental oncology (use of chemotherapy and targeted molecular therapy) have been made a huge progress in recent years, but the prognosis of lung cancer patients is still unsatisfactory or somewhat insufficient since the average 5-year survival rate for LC that includes adenocarcinoma is about 15% (5-7). Perhaps, the main reason of insufficient therapeutic efficacy is late stage diagnosis and rapid progress of LC. Therefore, scientists have been driven to identify development mechanism of LC and discover new therapeutic targets and agents including biomarkers.

Noncoding RNAs (ncRNAs), small (< 200 kb) and long (> 200 kb), have been recently shown to be involved in both tumor suppressive and oncogenic pathways (8-11). Long non-coding RNAs (lncRNAs) could be considered among biomarkers as they serve as molecular signals (12). They are involved in a wide variety of biological functions including facilitating or inhibiting the development and progression of tumors in LC (7). Hox transcript antisense intergenic RNA (HOTAIR, a human gene located on chromosome 12) is a type of lncRNA is expressed from the homebox C gene (HOXC) locus (13). HOTAIR is the very first example of an RNA expressed on one chromosome that has been discovered to stimulate transcription on another chromosome (14). There is growing evidence that show the overexpression of *HOTAIR* gene is highly associated with tumor cell proliferation, cell cycle, apoptosis regulation, tumor invasion, and progress and metastasis of various tumors and multiple cancer types including LC (13).

Hence, identification of the genes and single nucleotide polymorphisms (SNPs) within these genes is very important in order to determine increased genetic susceptibility of LC related to gene variants. The main aim of the current study was to investigate whether *HOTAIR* rs12826786 T>C and rs1899663 A>C polymorphisms could contribute to any role on susceptibility to LC in Turkish population. To best of our knowledge, there is no study have been conducted in determining the role of *HOTAIR* rs12826786 T>C and rs1899663 A>C polymorphisms in LC susceptibility in Turkey.

Materials and Methods

Ethics statement

The ethical approval was obtained from Hu-

man Ethics Committee (approval date and number: 21.05.2015/07) of Medical Faculty of Fırat University, Elazığ, Turkey. All the participants ensured their written informed consent to be included in the study concerning the use of their blood specimens for the current study. The study continued in agreement with the statement on the Declaration of Helsinki confirmed by the World Medical Association meeting in Edinburgh.

Study population

This hospital-based case–control study comprised a total of 180 men and women subjects including 87 (71 males 16 females) LC cases and 93 (67 males 26 females) healthy controls. Clinicopathological characteristics of all subjects are presented in Table 1. Informed consent about the study was taken from all the participants. All participants were over 18 years old and genetically unrelated Turkish people. The mean age value of the LC patients and healthy controls were 59.27±10.55 and 61.77±12.00, respectively. Healthy controls frequency was matched to LC cases on age and recruited from volunteers who came to the hospital for their routine check-ups. Controls were selected from people who have no evidence of any personal history of cancer or other malignant conditions. All LC cases were newly diagnosed, clinically and histologically confirmed with primary LC and were gathered from the Department of Thoracic Surgery between June 2015 and January 2018 from Adiyaman University Research and Education Hospital.Staging of LC was carried out according to the seventh edition of the International Association for the Study of Lung Cancer (IASLC) tumor–node–metastasis (TNM) staging system (15). All blood samples were taken from each patient before receiving any blood transfusion.

All clinical and pathological data of patients are taken as follows. Clinicopathological variables of LC patients including age, gender, smoking status, histologic type of cancer, and TNM stage were collected from the patients' medical records with the help of the surgeon.

Genotyping

Genotyping of *HOTAIR* rs12826786 T>C and rs1899663 A>C polymorphisms was performed by TaqMan allelic discrimination assay (TaqMan® SNP Genotyping Assay ID numbers for rs12826786: C__31185830_10 and for rs1899663: C___2104251_20) in accordance with protocols defined by the manufacturers (Applied Biosystems, Foster City, CA, USA). TaqMan real-time PCR reactions were performed with the LightCycler 96 instrument (Roche Diagnostics GmbH, Mannheim, Germany). The genotyping results were defined with endpoint genotyping analysis by LightCycler Genotyping software (Roche Diagnostics GmbH, Mannheim, Germany). Genotyping was carried out without knowledge of the case or control status. To ensure quality control of the study, a 10 % random sample of cases and controls was reciprocally tested by different researchers. The results of different researchers were found to be 100 % concordant, and all 87 LC patients and 93 healthy controls were finally included for subsequent statistical analyses.

Statistical analysis

Calculation of effective sample sizes for case–control study and to obtain 80 % power was done by Quanto (version 1.1) software (http://hydra.usc.edu/gxe) using minor allele frequency data from HapMap (http://hapmap.ncbi.nlm.nih.gov/) (16). Data analysis was performed using the computer software Statistical Package for Social Sciences (SPSS; SPSS, Inc., Chicago, IL, USA) version 16.0. Descriptive statistics of LC patients and controls in this study were presented as the mean ± SD for continuous variables, while frequencies (%) were used for categorical variables. Comparisons in the distributions of demographical characteristics between the patients with LC and healthy controls were evaluated using the Student's t test and Chi square (χ^2) test. The

Table 1. Clinical characteristics of non-small cell lung cancer cases and control subjects enrolled in current study.

Characteristic	Non-small cell lung cancer (n = 87)	Controls (n = 93)	*P*
Age (year, mean ± SD)	59.27 ± 10.55	61.77 ± 12.00	0.14
Gender			0.13
Males	71 (81.6 %)	67 (72.0 %)	
Females	16 (18.4 %)	26 (28.0 %)	
Smoking status			0.07
Smokers	61 (70.1 %)	53 (57.0 %)	
Non-smokers	26 (29.9 %)	40 (43.0 %)	
Histologic type of cancer			
Epidermoid carcinoma	46 (52.9 %)		
Adenocarcinoma	37 (42.5 %)		
Giant cell carcinoma	2 (2.3 %)		
Carcinoid tumor	2 (2.3 %)		
TNM stage of LC			
IA	13 (14.9 %)		
IB	8 (9.2 %)		
IIA	20 (23.0 %)		
IIB	16 (18.4 %)		
IIIA	19 (21.8 %)		
V	11 (12.6 %)		

observed genotype frequencies were compared with expected values calculated from Hardy–Weinberg equilibrium theory by 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) (17). Statistical analysis of genotypes was analyzed using the website for SNP Statistics: http://bioinfo.iconcologia.net/snpstats/start.htm (18). 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 any *P* value < 0.05 was considered as significant.

Results

Influence of HOTAIR rs12826786 T>C and rs1899663A>C polymorphisms

A total of 180 Turkish subjects (93 healthy controls and 87 LC patients) were genotyped in order to determine any possible association between LC and the genotypes of *HOTAIR* rs12826786 T>C and rs1899663 A>C polymorphisms. These polymorphisms were detected in the groups of LC cases and healthy control subjects as presented in Table 2. The distribution of *HOTAIR* polymorphisms genotypes in the healthy control groups were in accordance with Hardy-Weinberg expectation (P > 0.05 for both rs12826786 T>C and rs1899663A>C). In this study, the T allele of *HOTAIR* rs12826786 polymorphism was not associated with LC risk when compared with the C allele of *HOTAIR* rs12826786 (OR = 0.94, 95% CI 0.62-1.44, *P* = 0.87). Similarly, there was no statistical difference in codominant, dominant, and recessive genetic recessive models for *HOTAIR* rs12826786 polymorphism in terms of susceptibility to LC (Table 2). The A allele of *HOTAIR* rs1899663 polymorphism was not associated with LC risk when compared with the C allele of *HOTAIR* rs1899663 (OR = 1.02, 95% CI 0.66-1.58, *P* = 0.92).

Table 2. Allele and genotype frequencies in the non-small cell lung cancer cases and the healthy control groups as well as association of *HOTAIR* rs12826786 C>T and rs1899663 C>A polymorphisms with the risk of non-small cell lung cancer susceptibility according to different models of inheritance

	Controls n = 93 (%)	Non-small cell lung cancer n = 87 (%)	OR (95% CI)	*P*-value[a]	AIC[b]	BIC[c]
rs12826786						
Allele						
C	117 (62.9 %)	107 (61.5 %)	1.00 (Reference)			
T	69 (37.1 %)	67 (38.5 %)	0.94 (0.62-1.44)	0.87		
Codominant						
CC	38 (40.9 %)	33 (37.9 %)	1.00 (Reference)		255.1	264.7
CT	41 (44.1 %)	41 (47.2 %)	1.15 (0.61-2.18)	0.66		
TT	14 (15.0 %)	13 (14.9 %)	1.07 (0.44-2.60)	0.88		
Dominant						
CC	38 (40.9 %)	33 (37.9 %)	1.00 (Reference)		253.2	259.6
CT+TT	55 (59.1 %)	54 (62.1 %)	1.13 (0.62-2.06)	0.69		
Recessive						
CC+CT	79 (85 %)	74 (85.1 %)	1.00 (Reference)		253.3	259.7
TT	14 (15.0 %)	13 (14.9 %)	0.99 (0.44-2.25)	0.98		
Overdominant						
CC+TT	52 (55.9 %)	46 (52.9 %)	1.00 (Reference)		253.2	259.6
TT	41 (44.1 %)	41 (47.1 %)	1.13 (0.63-2.03)	0.68		
Log-additive	--	--	1.06 (0.70-1.61)	0.79	253.3	259.6
rs1899663						
Allele						
C	122 (65.6 %)	115 (66.1 %)	1.00 (Reference)			
A	64 (34.4 %)	59 (33.9 %)	1.02 (0.66-1.58)	0.92		
Codominant						
CC	41 (44.1 %)	39 (44.8 %)	1.00 (Reference)		255.3	264.9
CA	40 (43.0 %)	37 (42.5 %)	0.97 (0.52-1.82)	0.93		
AA	12 (12.9 %)	11 (12.6 %)	0.96 (0.38-2.44)	0.94		
Dominant						
CC	41 (44.1 %)	39 (44.8 %)	1.00 (Reference)		253.3	259.7
CA+AA	52 (55.9 %)	48 (55.2 %)	0.97 (0.54-1.75)	0.92		
Recessive						
CC+CA	81 (87.1 %)	76 (87.4 %)	1.00 (Reference)		253.3	259.7
AA	12 (12.9 %)	11 (12.6 %)	0.98 (0.41-2.35)	0.96		
Overdominant						
CC+AA	53 (57.0 %)	50 (57.5 %)	1.00 (Reference)		253.3	259.7
CA	40 (43.0 %)	37 (42.5 %)	0.98 (0.54-1.77)	0.95		
Log-additive	--	--	0.98 (0.64-1.50)	0.92	253.3	259.7

[a]Data were calculated by logistic regression analysis. [b]AIC: Akaike's information criterion. [c]BIC: Bayesian information criterion.

Table 3. Association of *HOTAIR* haplotypes with the risk of non-small cell lung cancer.

Haplotypes	Frequency		Healthy controls	Non-small lung cancer subjects	OR (95 % CI)	*P*-value
	rs12826786	rs1899663				
ht1	C	C	0.6290	0.5774	1.00 (Reference)	--
ht2	T	A	0.3441	0.3015	0.84 (0.53 - 1.34)	0.47
ht3	T	C	0.0269	0.0835	3.22 (1.12 - 9.22)	**0.03**

Global haplotype association *P*-value: 0.0016.

Additionally, the codominant, dominant, and recessive genetic recessive models of this polymorphism did not present any significance to be associated with LC risk. According to the results presented in Table 2, none of the of *HOTAIR* rs12826786 T>C and rs1899663 A>C polymorphisms showed statistical significance that can be related to LC in all of the genetic inheritance models.

Haplotype analysis

The total effect of the two *HOTAIR* polymorphisms (rs12826786 C>T and rs1899663 C>A) on the LC development was evaluated by haplotype analysis. Results of haplotype analysis are shown in Table 3. In total, three haplotypes were derived from the observed genotypes. The overall frequencies of haplotypes between LC patients and controls was statistically significant (P = 0.0016). Crs12826786/Crs1899663 (*ht1*) was the most common haplotype in LC cases and controls with frequencies of 0.6290 and 0.5774, respectively. Carriers of Trs12826786/Crs1899663 (*ht3*) had an increased risk of LC susceptibility (P = 0.03) while carriers of Trs12826786/Ars1899663 (*ht2*) do not seem to have any statistical significance (P = 0.47) of increased LC susceptibility risk.

Discussion

It has been known that Hox gene cluster is highly expressed in multiple tumors and lncRNAs, which are expressed from this gene, are considered as an emerging novel class of non-coding RNAs linked to the development of many diseases and cancers (19). There have been an increasing effort in order to determine the relationship between *HOTAIR* polymorphisms, lncRNAs, and the risk of human cancer. Many studies have been done on determining the effects of *HOTAIR* SNPs on various cancer types (such as pancreas (20), liver (21), gastric cancer (22-24), esophageal cancers (25,26), breast (27,28), colon (29), lung (30,31), laryngeal (32), nasopharyngeal [33]) in different populations. Since these studies represent confounding results that disagree with each other the interpretations of the phenotypic effects of these polymorphisms can be confusing and complicated (13).

According to a review and meta-analysis study, which was carried out by Min et al. (34), and our literature search seven *HOTAIR* polymorphisms were analyzed (rs7958904, rs4759314, rs874945, rs12826786, rs1899663, rs10783618 and rs920778) in over 30 enrolled case–control studies, while ten cancer types were reported. Among these studies, only four were about Turkish population and none of them was about LC (22,26,35,36). To the best of our knowledge, the current study is the first study that investigates a link between the *HOTAIR* rs12826786 T>C and rs1899663 A>C polymorphisms are contributing to any role on susceptibility to LC in Turkish population.

A study, which was performed on a northern Chinese population, by Guo et al. (37) reported that *HOTAIR* rs4759314 A > G and rs10783618 C > T polymorphisms did not have any effect on developing gastric cancer risk while the T allele of *HOTAIR* rs12826786 polymorphism increased it. And this SNP was associated with smoking habit and TNM stage. This result is in disagreement with the current study's result that suggests to no relationship between *HOTAIR* rs12826786 C>T polymorphism and susceptibility to LC. The controversy between these two studies could have also been generated due the studied different cancer types.

Ülger et al. (35) reported that there was a lack of any association between lncRNA *HOTAIR* rs12826786 C>T polymorphism and gastric cancer susceptibility in a Turkish population. Similarly, other two studies have suggested that *HOTAIR* rs920778 polymorphism did not contribute to any susceptibility in both gastric cancer and breast cancer in a Turkish population (26). Likewise, the results of this study suggested that neither *HOTAIR* rs12826786 C>T nor rs1899663 C>A polymorphisms was associated with the risk of lung cancer susceptibility.

Nagakawa et al. (30) concluded that enhanced *HOTAIR* expression in non-small cell lung cancer had been associated with advanced stage and short disease-free survival. Authors also stated that forced expression of this gene induced cell migration and anchorage-independent-cell growth *in vitro*, indicating that the evaluation of *HOTAIR* in non-small cell lung cancer samples could be a useful tool to predict the biological behavior of tumors, and potentially a therapeutic target in advanced non-small cell lung cancer. Gong et al. (12) studied eleven well-characterized lung cancer lncRNA polymorphisms with lung cancer susceptibility and platinum-based chemotherapy response. Authors found that some of the eleven lncRNA polymorphisms including *HOTAIR* rs7958904 and rs1899663 were significantly associated with lung cancer susceptibility or platinum-based chemotherapy response. The researchers concluded that the studied SNPs may be potential clinical markers to predict the risk of the development of lung cancer. Li et al. explored the possible relationships between *HOTAIR* polymorphisms rs920778, rs7958904, rs12826786, rs874945, and rs1899663 and cancer risk (39). The researchers identified that the rs12826786 polymorphism significantly increased susceptibility to cancer risk in all genetic models rather than heterozygous models. Our study disagrees with this results since we did not find any association between *HOTAIR* rs12826786 and LC risk. In addition, Li et al. (39) found no significant association between the rs1899663, rs874945, and rs4759314 polymorphisms

and susceptibility of cancer. However, the current study results agrees with Li et al. study in a way that is *HOTAIR* rs1899663 did not have any association with the development of LC risk (39).

In the current study, although allele and genotype frequencies in the non-small cell lung cancer cases and the healthy control groups did not contribute to any association of *HOTAIR* rs12826786 C>T and rs1899663 C>A polymorphisms with the risk of non-small cell lung cancer susceptibility (according to Table 2), the *HOTAIR* haplotype analysis suggested that there might be an association between haplotype ht3 and the risk of non-small cell lung cancer ($P = 0.03$) (according to Table 3). This result must be confirmed with further investigations in order to present convincing results.

There might be several possible limitations of the present case-control study and these should be taken into consideration. First, because it was a hospital-based case–control study and a large majority of LC cases and healthy controls were from the same hospital, inherent choice bias might be present. Therefore, it is crucial to verify the results of present study in population-based prospective study in the future. Secondly, the statistical strength of this study may be limited due to the sample size, particularly for statistical analyses of subgroups. In order to obtain more confidential results, prospective case-control studies with larger sample sizes should be performed to verify the association between *HOTAIR* rs12826786 and rs1899663 polymorphisms and LC risk. Thirdly, this hospital-based case-control study is also restricted by the Turkish ethnicity and local population because discrepancies in allele frequency have been ascertained for *HOTAIR* rs12826786 and rs1899663 polymorphisms in the different populations. Further studies on different populations of the same ethnicity and different ethnicities are needed to obtain convincing results in order to better evaluate the association between *HOTAIR* rs12826786 and rs1899663 polymorphisms and LC risk.

In conclusion, our findings suggest that the *HOTAIR* rs12826786 and rs1899663 polymorphisms have not played any major role in genetic susceptibility to non-small cell lung cancer susceptibility within the Turkish population. Further well designed independent studies are required to validate our findings in a larger series and samples sizes, as well as in patients of different ethnic origins to better understand *HOTAIR* rs12826786 and rs1899663 polymorphisms and susceptibility to LC.

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Conflict of interest
Authors declare no conflict of interests.

Author's contribution
Concept: Erdoğan Dadaş; Data collection and/or processing: Erdoğan Dadaş; Literature Review and Writing: Erdoğan Dadaş (head-writer) and Muhsin Aydın.

References

1. Liu W, Yin NC, Liu H, Nan KJ. Cav-1 promote lung cancer cell proliferation and invasion through lncRNA HOTAIR. Gene. 2018; 641: 335–40.
2. Siegel RL, Naishadham D, Jemal A. Cancer statistics, 201. CA Cancer J Clin. 2012; 62: 10-29.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66: 7–30.
4. Popper HH. Progression and metastasis of lung cancer. Cancer Metastasis Rev. 2016; 35: 75–91.
5. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, Kunkler I, and EUROCARE-4 Working Group. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE- 4 data. Lancet Oncol. 2007; 8: 784–96.
6. Reck M, Heigener DF, Mok T, Soria JC, Rabe KF. Management of non-small-cell lung cancer: recent developments. Lancet. 2013; 382, 709–19.
7. Chen J, Wang R, Zhang K, Chen L-B. Long non-coding RNAs in non-small cell lung cancer as biomarkers and therapeutic targets. J Cell Mol Med. 2014; 18(12): 2425-36.
8. Brosnan CA, voinnet O. The long and the short of noncoding RNAs. Curr Opin Cell Biol. 2009; 21: 416-25.
9. Moazed D. Small RNAs in transcriptional gene silencing and genome defence. Nature 2009; 457: 413-20.
10. Malone CD, Hannon GJ. Small RNAs as guardians of the genome. Cell. 2009; 136: 656-68.
11. Zhao W, An Y, Liang Y, Xie XW. Role of HOTAIR long noncoding RNA in metastatic progression of lung cancer. Eur Rev Med Pharmacol Sci. 2014; 18(13): 1930-6.
12. Gong WJ, Yin JY, Li XP, Fang C, Xiao D, Zhang W, Zhou HH, Li Xi, Liu ZQ. Association of well-characterized lung cancer lncRNA polymorphisms with lung cancer susceptibility and platinum-based chemotherapy response. Tumour Biol. 2016; 37(6): 8349-58.
13. Tao T, Li G, Zhang X, Guan H, Huang Y, Chen M. Association between LncRNA HOTAIR rs4759314 A > G polymorphism and cancer risk: a meta-analysis based on 5525 cases and 6657 controls in Chinese populations. Int J Clin Exp Med 2016; 9(7): 12780-7.
14.GeneCards.https://www.genecards.org/cgi-bin/carddisp.pl?gene=HOTAIR (Accessed on March 10, 2018).
15. Goldstraw P, ed. 7th edition of TNM for lung and pleural tumors. In: IASLC Staging Manual in Thoracic Oncology. Orange Park-FL, Editorial Rx Press, 2009; 58-65.
16. Gauderman WJ, Morrison JM. Quanto 1.1: A computer program for power and sample size calculations for genetic-epidemiology studies. 2006. http://hydra.usc.edu/gxe (Accessed on January 20, 2018).
17. Rodriguez S, Gaunt TR, Day IN. Hardy–Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies. Am J Epidemiol. 2009; 169(4): 505–14.
18. Sole´ X, Guino´ E, Valls J, Iniesta R, Moreno V. SNPStats: a web tool for the analysis of association studies. Bioinformatics. 2006; 22(15): 1928–9.
19. Wapinski O, Chang HY. Long noncoding RNAs and human disease. Trends Cell Biol. 2011; 21: 354-61.
20. Kim K, Jutooru I, Chadalapaka G, Johnson G, Frank J, Burghardt R, Kim S, Safe S. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. Oncogene. 2013; 32: 1616-25.
21. Geng YJ, Xie SL, Li Q, Ma J, Wang GY. Large intervening noncoding RNA HOTAIR is associated with hepatocellular carcinoma progression. J Int Med Res. 2011; 39: 2119-28.
22. Niinuma T, Suzuki H, Nojima M, Nosho K, Yamamoto H, Takamaru H, Yamamoto E, Association between LncRNA HOTAIR

rs4759314 A > G polymorphism and cancer risk 12787 Int J Clin Exp Med. 2016; 9(7): 12780-7.
23. Maruyama R, Nobuoka T, Miyazaki Y, Nishida T, Bamba T,Kanda T, Ajioka Y, Taguchi T, Okahara S, Takahashi H, Nishida Y, Hosokawa M, Hasegawa T, Tokino T, Hirata K, Imai K, Toyota M, Shinomura Y. Upregulation of miR-196a and HOTAIR drive malignant character in gastrointestinal stromal tumors. Cancer Res. 2012; 72: 1126-36.
24. Hajjari M, Behmanesh M, Sadeghizadeh M, Zeinoddini M. Up-regulation of HOTAIR long non-coding RNA in human gastric adenocarcinoma tissues. Med Oncol. 2013; 30: 670.
25. Bayram S, Ulger Y, Sumbul AT, Kaya BY, Rencüzoğulları A, Genç A, Sevgiler Y, Bozkurt O, Rencüzoğulları E. A functional HOTAIR rs920778 polymorphism does not contributes to gastric cancer in a Turkish population: a case-control study. Fam Cancer. 2015; 14:561-7.
26. Li X, Wu Z, Mei Q, Li X, Guo M, Fu X, Han W. Long non-coding RNA HOTAIR, a driver of malignancy, predicts negative prognosis and exhibits oncogenic activity in oesophageal squamous cell carcinoma. Br J Cancer. 2013; 109: 2266-78.
27. Chen FJ, Sun M, Li SQ, Wu QQ, Ji L, Liu ZL, Zhou GZ, Cao G, Jin L, Xie HW, Wang CM, Lv J, De W, Wu M, Cao XF. Upregulation of the long non-coding RNA HOTAIR promotes esophageal squamous cell carcinoma metastasis and poor prognosis. Mol Carcinog. 2013; 52: 908-15.
28. Chisholm KM, Wan Y, Li R, Montgomery KD, Chang HY and West RB. Detection of long noncoding RNA in archival tissue: correlation with polycomb protein expression in primary and metastatic breast carcinoma. PLoS One 2012; 7: e47998.
29. Bayram S, Sumbul AT, Batmaci CY and Genc A. Effect of HOTAIR rs920778 polymorphism on breast cancer susceptibility and clinicopathologic features in a Turkish population. Tumour Biol. 2015; 36: 3863-70.
30. Kogo R, Shimamura T, Mimori K, Kawahara K, Imoto S, Sudo T, Tanaka F, Shibata K, Suzuki A, Komune S, Miyano S, Mori M. Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. Cancer Res. 2011; 71: 6320-26.
31. Nakagawa T, Endo H, Yokoyama M, Abe J, Tamai K, Tanaka N, Sato I, Takahashi S, Kondo T, Satoh K. Large noncoding RNA HOTAIR enhances aggressive biological behavior and is associated with short disease-free survival in human non-small cell lung cancer. Biochem Biophys Res Commun. 2013; 436: 319-24.
32. Liu XH, Liu ZL, Sun M, Liu J, Wang ZX and De W. The long non-coding RNA HOTAIR indicates a poor prognosis and promotes metastasis in non-small cell lung cancer. BMC Cancer. 2013; 13: 464.
33. Li D, Feng J, Wu T, Wang Y, Sun Y, Ren J, Liu M. Long intergenic noncoding RNA HOTAIR is overexpressed and regulates PTEN methylation in laryngeal squamous cell carcinoma. Am J Pathol 2013; 182: 64-70.
34. Nie Y, Liu X, Qu S, Song E, Zou H and Gong C. Long non-coding RNA HOTAIR is an independent prognostic marker for nasopharyngeal carcinoma progression and survival. Cancer Sci 2013; 104: 458-64.
35. Min L, Mu X, Tong A, Qian Y, Ling C, Yi T, Zhao X. The association between HOTAIR polymorphisms and cancer susceptibility: an updated systemic review and meta-analysis. Oncol Targets Ther. 2018; 11: 791-800.
36. Ülger Y, Dadaş E, Yalinbaş Kaya B, Sümbül AT, Genç A, Bayram S. 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. Ir J Med Sci. 2017; 186: 859-65.
37. Bayram S, Sumbul AT, Dadas E. A functional HOTAIR rs12826786 C.T polymorphism is associated with breast cancer susceptibility and poor clinicopathological characteristics in a Turkish population: a hospital-based case-control study. Tumor Biol. 2016; 37(4): 5577–84.
38. Guo W, Dong Z, Bai Y, Guo Y, Shen S, Kuang G, Xu J. Associations between polymorphisms of HOTAIR and risk of gastric cardia adenocarcinoma in a population of north China. Tumor Biol 2015: 36: 2845-54.
39. Li J, Cui Z, Li H, Lv X, Gao M, Yang Z, Bi Y, Zhou B, Yin Z. Long non-coding RNA HOTAIR polymorphism and susceptibility to cancer: an updated meta-analysis. Environ Health Prev Med. 2018; 23:8.