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Association Between HOTAIR rs920778 and H19 rs3741219 Polymorphisms with Hashimoto's Thyroiditis (HT) and Graves' Disease (GD)

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Abstract

Background: Graves' disease (GD) and Hashimoto's thyroiditis (HT) are two autoimmune thyroid diseases (AITDs). The current study aimed to assess possible association between HOTAIR rs920778 and H19 rs3741219 polymorphisms with GD and HT.

Methods: We recruited 248 patients with autoimmune thyroid disease (133 HT patients and 115 GD patients) and 135 age- and sex-matched controls. The PCR-RFLP method was applied for genotyping of HOTAIR rs920778, and H19 rs3741219 polymorphisms.

Results: The HOTAIR rs920778 GA frequency was significantly higher in control compared to HT group. The Overdominant model showed a significant association with the risk of HT. However, no significant association was observed between this polymorphism and HT susceptibility in dominant and recessive models. The H19 rs3741219 GA was more repeated in HT patients compared to control group, but the difference was not significant. There was no association between HOTAIR rs920778 and H19 rs3741219 polymorphisms with GD in all genetic models.

Conclusions: Our findings indicated that HOTAIR rs920778 polymorphism decreased the risk of HT. Since, this the first study, further studies with different races are required to confirm our results.

Keywords: Hashimoto's thyroiditis, Graves' disease, HOTAIR; H19, Polymorphism.

Introduction

Autoimmune thyroid diseases (AITDs) include endocrine autoimmune conditions with a fluctuating distribution among various races and in the regions with a different quantity of iodine consumption (1). Graves' disease (GD) and Hashimoto's thyroiditis (HT) are primarily two disease forms of AITDs (2). As for the GD, the level of thyroid-stimulating hormone (TSH) receptor antibody (TRAb) is abnormally elevated, which attaches to the TSH receptor (TSHR) on thyroid follicular cells with TSH, thereby enhancing the production and releasing of thyroid hormones (2). Although the exact cause of GD is still unknown, the findings emphasize the central role of both genetic and environmental factors (3). In the case of HT as the most prevalent inflammatory thyroid disorder, the levels of thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TGAb) increase abnormally. A hypothyroidism occurs in the HT in the clinics and clinical manifestations can be observed contradictory to the GD; the prevalence of HT is higher in middle-aged females. Although the HT has unclear etiology so far, but family aggregation that is frequently observed among the same family generations has been recognized in this disease (4).

Long non-coding RNAs or lncRNAs belong to the non-coding RNA family which are found in abundance in eukaryotic

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transcriptome, with a length of more than 200 nucleotides (5). According to solid evidence, lncRNAs have a strong correlation with the development of immune system and the regulation of functions. Moreover, the lncRNAs are engaged to regulate the formation and differentiation of T cells, and certain lncRNAs may be specifically expressed by various T cells (6). The recent findings reported that the dysregulation of lncRNAs may influence autoimmune disorders like systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, etc (7, 8). On the other hand, the exact role of lncRNAs in causing autoimmune disorders remains unclear (6).

A conventional lncRNA that pertains to the homeobox superfamily is named HOX transcript antisense intergenic RNA (HOTAIR). The transcription of HOTAIR occurs from the locus of HOXC located at the opposite direction, comprises of 2158 nucleotides on chromosome 12q13.13 (9). The H19 is a lncRNA on chromosome 11p15.5 and its length is nearly 2.3-kb (10). The maternal imprinted and expressed *H19* gene, and it performs an interchangeably function in the embryonic stage with reduced levels in mature postpartum tissues (11).

To the best of our knowledge, no study has existed that demonstrated the possible associations of HOTAIR and H19 polymorphisms with AITD. Therefore, in this study, we examined the role of HOTAIR rs920778 and H19 rs3741219 polymorphisms in AITD.

Materials and Methods

Ethical approval

All proceeding performed in the present study containing human participants were conforming to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consents were gained from the study subjects. Also, the study protocol was approved by the ethics committee of Zahedan University of Medical Science.

Study subjects

The current case-control study contains 248 patients with AITD (133 HT patients and 115 GD patients) and 135 age- and gender-matched controls. Clinical manifestations and laboratory profiles were used to diagnose AITDs patients referred to Ali-ebn Abitaleb Hospital, Zahedan, South-East Iran, by an endocrinologist. The study excluded patients with other autoimmune diseases but not AITD. Healthy individuals who visited the same hospital for a checkup were selected as controls as they did not have past or family histories of any autoimmune diseases. The Ethics Committee of the Zahedan University of Medical Sciences approved the study protocol, and all participants provided written consent.

DNA extraction and genotype analysis

Genomic DNA was extracted using salting-out protocol. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was applied for genotyping of HOTAIR rs920778, and H19 rs3741219. The primer sequences are reported in Table 1 (12, 13). The PCR amplification reaction conditions were as follows: initial denaturation at 95 °C for 2 min followed by 30 cycles of denaturation at 95 °C for 30 s, annealing temperature at 55 °C during 30 s for HOTAIR, at 62 °C during 30 s for H19, and extension at 72 °C for 30 s, and final extension at 72 °C for 3 min. The PCR products of HOTAIR rs920778, and H19 rs3741219 polymorphisms were digested with *MspI* and *HhaI* restriction enzymes, respectively and separated on a 2% agarose gel.

Statistical analysis

IBM SPSS version 23.0 was utilized for

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statistical analysis. Chi-square test (X^2) test and independent sample t-test was used to evaluate the categorical and continuous variables, respectively. In order to determining the effect of each polymorphism on HT and GD, the logistic regression method was applied. p-value< 0.05 was defined statistically significant.

Table1. Primers and restriction enzymes used for RFLP-PCR.

Gene and SNP number	Primers	Digested fragments size (bp)
HOTAIR (rs920778)	F: TTACAGCTTAAATGTCTGAATGTTCC R: TATGCGCTTTGCTTCCAGTT	T= 234 C= 26+208
H19 (rs3741219)	F: CCCCCTGCGGCGGACGGTTGA R: GGCGTAATGGAATGCTTGAA	A= 434 G= 299 + 135

F: Forward, R: Reverse.

Results

The demographic and clinical characteristics of patients (HT and GD) and control groups

The mean age of HT and GD patients and control group were 35.3±1.023, 35.8±1.11, and 37.2±1.07, respectively. Regarding to age variables, no significant differences between patient groups and control group was found. The frequency of females was higher than males in HT, GD, and control groups. The mean onset age of HT and GD patients were 31.34±0.89 and 34.73±1.11, respectively. The family history was 29.3% and 27.8% in HT and GD groups, respectively. The mean BMI of HT and GD patients were 26.93±0.49 and 21.9±0.44, respectively. In HT group the mean levels of THS, T4, and T3 were 62.1±2.5, 0.478±0.01, and 1.16±0.033. In GD group the mean levels of THS, T4, and T3 were 0.016±0.002, 3.15±0.11, and 6.7±0.19.

The genotypic and allelic frequencies of HOTAIR and H19 genes SNPs in the HT and control groups

The genotypic and allelic frequencies of *HOTAIR* and *H19* genes SNPs in the HT and control groups are presented in Table 2. The HOTAIR rs920778 GA frequency was significantly greater in control compared to HT group (51.8% vs 34.6% p= 0.028, OR= 0.52, 95% CI= 0.29-0.93). The Overdominant model showed a significant association with the risk of HT (OR= 0.48, 95%CI= 0.29–0.78, p= 0.003, GA *vs.* GG+ AA). However, the results showed that HOTAIR rs920778 polymorphism was not accompanied with HT susceptibility in dominant (OR= 0.72, 95%CI= 0.42–1.22, *P*= 0.229, GA+ AA *vs.* GG) and recessive (OR= 1.75, 95%CI= 1.01–3, p= 0.054, AA *vs.* GG+ GA) models. Indeed, no association was observed between allelic frequency and HT risk (OR= 1.06, 95%CI= 0.75–1.48, p= 0.795).

As shown in Table 2, the H19 rs3741219 GA frequency was higher in HT patients compared to control group (48.9 vs. 48.1%), but the difference was not significant (p=0.814, OR= 0.94, 95% CI= 0.56-1.5). There was also no relationship between H19 rs3741219 polymorphism and HT risk under the dominant, recessive, and overdominant models. The allelic distribution also showed no significant difference.

The genotypic and allelic frequencies of HOTAIR and H19 genes SNPs in the GD and control groups

Table 3 presents the genotypic and allelic frequencies of *HOTAIR* and *H19* polymorphisms in the GD and control groups. The HOTAIR rs920778 AA frequency was higher in GD patients compared to control group (33 vs. 22.2%), but the difference was not significant (p= 0.134, OR= 1.7, 95% CI= 0.84-3.4). Our findings also showed no association between HOTAIR rs920778 polymorphism and GD in dominant, recessive, and overdominant models. There was no significant difference between the GD and control groups under the allelic distribution. No significant relationship was found between

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H19 rs3741219 polymorphism and GD risk in all genetic models.

Relationship between H19 rs3741219 and HOTAIR rs920778 polymorphisms and clinical and demographic characteristics of patients with GD and HT

As observed in Table 4, there was a significant relationship between the recessive model of H19 rs3741219 polymorphism and the anti-Tg level in the HT group. In patients with HT, HOTAIR rs920778 polymorphism was associated with BMI in the dominant model. In GD group, dominant and recessive models of H19 rs3741219 polymorphism were significantly associated with age of incidence and TSH levels, respectively. Besides, dominant, and recessive models of HOTAIR rs920778 polymorphism were significantly related to TSH levels.

Table 2. Allelic and genotypic frequency of HOTAIR rs920778 and H-19 rs3741219 polymorphisms in Hashimoto's thyroiditis (HT) and control groups.

Polymorphism	HT number (%)	Control number (%)	P-value	OR (95%CI)
HOTAIR rs920778				
Codominant				
GG	44 (33)	35 (26)		1
GA	46 (34.6)	70 (51.8)	0.028	0.52 (0.29-0.93)
AA	43 (32.4)	30 (22.2)	0.589	1.19 (0.62-2.26)
Dominant				
GG	44 (33)	35 (26)		1
GA+AA	86 (67)	100 (74)	0.229	0.72 (0.42-1.22)
Recessive				
GG+GA	86 (67.6)	105(77.8)		1
AA	43 (32.4)	30 (22.2)	0.054	1.75 (1.01-3)
Overdominant				
GG+AA	87 (65.4)	75 (48.2)		1
GA	46 (34.6)	70 (51.8)	0.003	0.48 (0.29-0.78)
Allele				
G	134 (50.3)	140 (51.8)		1
A	132 (49.7)	130 (48.2)	0.795	1.06 (0.75-1.48)
H-19 rs3741219				
Codominant				
AA	54 (40)	50 (37)		1
GA	66 (48.9)	65 (48.1)	0.814	0.94 (0.56-1.5)
GG	15 (11.1)	20 (14.9)	0.355	0.69 (0.32-1.5)
Dominant				
AA	54 (40)	50 (37)		1
GA+GG	76 (60)	85 (63)	0.617	0.88 (0.54-1.4)
Recessive				
AA+GA	120 (88.9)	115(85.1)		1
GG	15 (11.1)	20 (14.9)	0.366	0.71 (0.35-1.5)
Overdominant				
GG+AA	69 (51.1)	70 (51.9)		1
GA	66 (48.9)	65 (48.1)	0.366	0.71 (0.35-1.5)
Allele				
A	174 (64.5)	165 (61.1)		1
G	96 (35.5)	105 (38.9)	0.476	0.86 (0.61-1.2)

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Table 3. Allelic and genotypic frequency of HOTAIR rs920778 and H-19 rs3741219 polymorphisms in Graver's disease (GD) and control groups.

Polymorphism	GD number (%)	Control number (%)	P-value	OR (95%CI)
HOTAIR rs920778				
Codominant				
GG	26 (22.6)	35 (26)		1
GA	51 (44.4)	70 (51.8)	0.951	0.98 (0.52-1.8)
AA	38 (33)	30 (22.2)	0.134	1.7 (0.84-3.4)
Dominant				
GG	26 (22.6)	35 (26)		1
GA+AA	89 (77.4)	100 (74)	0.543	1.19 (0.67-2.14)
Recessive				
GG+GA +GA	57 (67)	105(77.8)		1
AA	38 (33)	30 (22.2)	0.057	1.7 (0.88-3)
Overdominant				
GG+AA	64 (55.6)	75 (48.2)		1
GA	51 (44.4)	70 (51.8)	0.237	0.74 (0.45-1.2)
Allele				
G	103 (44.8)	140 (51.8)		1
A	127 (55.2)	130 (48.2)	0.127	1.3 (0.93-1.89)
H-19 rs3741219				
Codominant				
AA	44 (38.2)	50 (37)		1
GA	46 (40)	65 (48.1)	0.441	0.8 (0.46-1.4)
GG	25 (21.8)	20 (14.9)	0.335	1.4 (0.7-2.9)
Dominant				
AA	44 (38.2)	50 (37)		1
GA+GG	71 (61.8)	85 (63)	0.842	0.94 (0.56-1.5)
Recessive				
AA+GA +GA	90 (78.2)	115(85.1)		1
GG	25 (21.8)	20 (14.9)	0.158	1.5 (0.83-3)
Overdominant				
GG+AA	69 (60)	70 (51.9)		1
GA	46 (40)	65 (48.1)	0.197	0.71 (0.35-1.5)
Allele				
A	134 (58.2)	165 (61.1)		1
G	96 (41.8)	105 (38.9)	0.583	1.1 (0.77-1.6)

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Table 4. Association of HOTAIR rs920778 and H19 rs3741219 SNPs with clinical and demographic characteristics of HT and GD groups.

Group	Mean±SEM			P-value				
				Codominant		Dominant	Recessive	Overdominant
HT								
rs3741219	**AA**	**AG**	**GG**	**AA vs GA**	**AA vs GG**	**AA vs GA+GG**	**AA+GA vs +GG**	**AA+ GG vs +GA**
Anti-Tg	624.7±142.3	636.6±142.4	1404.6±658.3	0.99	0.116	0.513	*0.036*	0.5
rs920778	**GG**	**GA**	**AA**	**GG vs GA**	**GG vs AA**	**GG vs GA+AA**	**GG+GA vs AA**	**GG+AA vs GA**
BMI	25.38±0.79	27.6±0.9	27.7±0.8	0.149	0.127	*0.028*	0.25	0.309
GD								
rs3741219	**AA**	**GA**	**GG**	**AA vs GA**	**AA vs GG**	**AA vs GA+GG**	**AA+GA vs GG**	**GG+AA vs GA**
Age of onset	31.8±1.6	36.9±1.8	35.6±2.4	0.104	0.411	*0.041*	0.668	0.099
TSH	0.0189±0.004	0.01804±0.004	0.0752±0.002	0.989	0.275	0.423	*0.008*	0.565
rs920778	**AA**	**GA**	**GG**	**AA vs GA**	**AA vs GG**	**AA vs GA+GG**	**AA+GA vs GG**	**GG+AA vs GA**
TSH	0.0067±0.001	0.01771±0.004	0.02029±0.005	0.274	0.172	*0.003*	*0.008*	0.603

Discussion

Our results showed that the HOTAIR rs920778 GA frequency was significantly greater in control compared to HT group. The Overdominant model of the HOTAIR rs920778 also showed a significant association with the risk of HT. There was no relationship between H19 rs3741219 polymorphism and HT risk. Our findings also showed no association between HOTAIR rs920778 polymorphism and GD development risk. Finally, no significant relationship was found between H19 rs3741219 polymorphism and GD risk in all genetic models.

As reported by studies, expression of HOTAIR is significantly higher in PBMC of Rheumatoid arthritis (RA) patients (14, 15). Our findings indicated that the frequency of GA genotype of HOTAIR rs920778 gene polymorphism was significantly higher in the control group compared to HT group, and this genotype probably has a protective effect against HT. Moreover, no significant differences were observed between the polymorphisms of the HOTAIR gene between the control and GD groups. According to our information, this is the first report on the impact of HOTAIR rs920778 polymorphism on autoimmune thyroid disorders. Functional variants can influence expression of genes. Zhang et al. in the *in vitro* and *in vivo* models of ESCC cancer demonstrated that the T allele of HOTAIR rs920778 polymorphism increases its expression (16). Studies have reported a relationship between this polymorphism and cancers such as breast cancer, colorectal cancer, and hepatocellular carcinoma (17-19), which in some cases was associated with race and disease severity (19, 20). Zhu et al. suggested the oncogenic behavior of HOTAIR in Papillary carcinoma (PTC) and indicated the higher expression of HOTAIR in PTC tissue than in healthy tissue. They also observed that carriers of the TT genotype of HOTAIR rs920778 had a higher risk of incidence of PTC than the CC genotype. Interestingly, they found this association only in women with PTC. In men, they reported an association between this polymorphism and autoimmune disorders (21). Huang et al. reported a lack of association between HOTAIR rs920778 gene polymorphism with autoimmune disorders, including SLE and RA and Sjögren's syndrome (22).

Considering the H19 rs3741219 gene polymorphism, no significant relationship was found between this polymorphism and HT and GD risk. Chen et al. reported that H19 could inhibit immune dysregulation in bone marrow-driven mesenchymal stem cells (BMMSCs) in patients with Systemic lupus erythematosus (SLE) by inhibiting IL-2 production, and they proposed H19 as a new therapeutic target in SLE

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(23). Yang et al studied MH7A cells in order to investigated impact of H19 on RA and found that H19 had inflammatory effects in these cells, so that treatment of these cells with tumor necrosis factor alpha (TNF-α) increased expression of H19 expression. Besides, they observed that inhibition of H19 expression decreased the level of inflammatory cytokines and increased its expression showed an opposite effect (24). Stuhlmuller et al. indicated H19-induced expression in the synovial tissue of RA patients (25). While Wu et al. observed reduced expression of H19, GAS5, and linc0597 in PBMC in RA patients. They also did not find any association between rs2067051 and rs2075745 polymorphisms of H19 gene and RA susceptibility (26). Huang et al. concluded that there was no association between H19 rs2839698 and rs3741219 polymorphisms with autoimmune disorders, such as SLE and RA (22). Wang et al. studied the impact of H19 gene polymorphisms on osteoarthritis and found that rs3741219 was not associated with the risk of Osteoarthritis (OA), while the A allele of H19 rs217727 polymorphism increased the risk of infection (27). The effect of H19 gene polymorphisms on disorders such as cancer has been investigated. In a meta-analysis study by Hashemi et al. it was found that H19 rs217727 C> T polymorphism was associated with cancer risk, while H19 polymorphisms: rs2839698 G> A, rs2107425 C> T, rs2735971 C> T, rs3024270 G> C, rs3741219 T> C, rs2839701 C> G, rs2735469 C> T, rs17658052 G> A, and rs3741216 T> A did not show such effect (10). There is little information available on the effect of H19 rs3741219 polymorphism on the expression and function of H19. Song et al. in a study on hepatocellular carcinoma (HCC) cells concluded that the C allele of this polymorphism decreases expression of H19 through creating a binding site for miR-146b-3p and miR1539 (28).

Our findings indicated the association between H19 rs3741219 gene polymorphisms and HOTAIR rs920778 gene polymorphisms with such properties as age, TSH, and anti-Tg levels, and BMI.

This is the first research studying the association between H19 rs3741219 and HOTAIR rs920778 polymorphisms and the demographic and clinical characteristics of AITD patients. However, there are some studies that have investigated the association between the polymorphisms of some genes and these characteristics. For example, He et al. observed a significant association between the dominant model of CD160 rs744877 polymorphism and gender in AITD (1). Zaaber et al. reported that the TC genotype of TSHR rs74067403 polymorphism was associated with the age of incidence of AITD (29). Heidari et al. found a significant relationship between NLRP3 polymorphism and anti-TPO level in HT group and FT4 and FT3 levels in GD group. Their results also demonstrated an association between IL-1β polymorphism and age of incidence of HT and TSH levels in GD. They indicated that TSH levels were also associated with COX-2 polymorphism in patients with GD (30).

In conclusion, our results showed that the HOTAIR rs920778 GA frequency was significantly greater in control compared to HT group. The Overdominant model of the HOTAIR rs920778 also showed a significant association with the risk of HT. There was no relationship between H19 rs3741219 polymorphism and HT risk. Our findings also showed no association between HOTAIR rs920778 polymorphism and GD development risk. Finally, no significant relationship was found between H19 rs3741219 polymorphism and GD risk in all genetic models. Since, this the first study, further studies with different races are required to confirm our results.

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References

1. He W, Zhao J, Liu X, Li S, Mu K, Zhang J, et al. Associations between CD160 polymorphisms and autoimmune thyroid disease: a case-control study. 2021;21(1):148.
2. Liu X, Bai X, Zhao J, Gao C, Du P, Zhang J-a, et al. Associations between NLRC4 gene polymorphisms and autoimmune thyroid disease. Biomed Res Int. 2020;2020:1378427.
3. Li H-n, Li X-r, Du Y-y, Yang Z-f, Lv Z-tJFie. The association between Foxp3 polymorphisms and risk of Graves' disease: a systematic review and meta-analysis of observational studies. Front Endocrinol (Lausanne). 2020;11:392.
4. He W, Wang B, Mu K, Zhang J, Yang Y, Yao W, et al. Association of single-nucleotide polymorphisms in the IL27 gene with autoimmune thyroid diseases. 2019;8(3):173-81.
5. Shaker O, Mahfouz H, Salama A, Medhat E. Long Non-Coding HULC and miRNA-372 as Diagnostic Biomarkers in Hepatocellular Carcinoma patients. rbmb. 2020;9(2):230-240.
6. Yin L, Zeng C, Yao J, Shen JJE. Emerging roles for noncoding RNAs in autoimmune thyroid disease. Endocrinology. 2020;161(8):bqaa053.
7. Wang J, Wei F, Zhou HJFiLM. Advances of lncRNA in autoimmune diseases. Frontiers in Laboratory Medicine. 2018;2(2):79-82.
8. Medhat E, Ayeldeen G, Hosni Ahmed H, Shaker O, Gheita T, Salama Ashour S. HOTAIR and THRIL Long Non Coding RNAs and Their Target Genes in Rheumatoid Arthritis patients. Rep Biochem Mol Biol. 2022;10(4):614-621.
9. Salimi S, Sargazi S, Heidari Nia M, Mirani Sargazi F, Ghasemi MJJoO, Research G. Genetic variants of HOTAIR are associated with susceptibility to recurrent spontaneous abortion: A preliminary case–control study. 2021;47(11):3767-3778.
10. Hashemi M, Moazeni-Roodi A, Sarabandi S, Karami S, Ghavami SJJoG. Association between genetic polymorphisms of long noncoding RNA H19 and cancer risk: a meta-analysis. 2019;98:81.
11. Wang K, Zhu Z, Wang Y, Zong D, Xue P, Gu J, et al. The influence of LncRNA H19 polymorphic variants on susceptibility to cancer: A systematic review and updated meta-analysis of 28 case-control studies. PLoS One. 2021;16(7):e0254943.
12. Xavier-Magalhães A, Oliveira AI, de Castro JV, Pojo M, Gonçalves CS, Lourenço T, et al. Effects of the functional HOTAIR rs920778 and rs12826786 genetic variants in glioma susceptibility and patient prognosis. J Neurooncol. 2017;132(1):27-34.
13. Xia Z, Yan R, Duan F, Song C, Wang P, Wang K. Genetic Polymorphisms in Long Noncoding RNA H19 Are Associated With Susceptibility to Breast Cancer in Chinese Population. Medicine (Baltimore). 2016;95(7):e2771.
14. Song J, Kim D, Han J, Kim Y, Lee M, Jin E-JJC, et al. PBMC and exosome-derived Hotair is a critical regulator and potent marker for rheumatoid arthritis. 2015;15(1):121-6.
15. Shaker OG, Mahmoud RH, Abdelaleem OO, Ahmed TI, Fouad NA, Hussein HA, et al. Expression profile of long noncoding RNAs, lnc-Cox2, and HOTAIR in rheumatoid arthritis patients. 2019;39(3):174-180.
16. Zhang X, Zhou L, Fu G, Sun F, Shi J, Wei J, et al. The identification of an ESCC susceptibility SNP rs920778 that regulates the expression of lncRNA HOTAIR via a novel intronic enhancer. 2014;35(9):2062-7.
17. Lv Z, Kou C, Chen N, Jia L, Sun X, Gao Y, et al. Single Nucleotide Polymorphisms in HOTAIR Are Related to Breast Cancer Risk and Prognosis in the Northeastern Chinese Population. 2021;11:706428.
18. Li H, Tang X-M, Liu Y, Li W, Chen Q, Pan YJCP, et al. Association of functional genetic variants of HOTAIR with hepatocellular carcinoma (HCC) susceptibility in a Chinese population. 2017;44(2):447-454.
19. Kim JO, Jun HH, Kim EJ, Lee JY, Park HS, Ryu CS, et al. Genetic variants of *HOTAIR* associated with colorectal cancer susceptibility and mortality. 2020;10:72.
20. Qi Q, Wang J, Huang B, Chen A, Li G, Li X, et al. Association of HOTAIR polymorphisms rs4759314 and rs920778 with cancer susceptibility on the basis of ethnicity and cancer type. 2016;7(25):38775-38784.
21. Zhu H, Lv Z, An C, Shi M, Pan W, Zhou L, et al. Onco-lncRNA HOTAIR and its functional

[DOI: 10.52547/rbmb.11.3.377]

genetic variants in papillary thyroid carcinoma. Sci Rep. 2016;6:31969.
22. Huang A-F, Su L-C, Jia H, Liu Y, Xu W-DJCR. No association of single nucleotide polymorphisms within H19 and HOX transcript antisense RNA (HOTAIR) with genetic susceptibility to systemic lupus erythematosus, rheumatoid arthritis, and primary Sjögren's syndrome in a Chinese Han population. Clin Rheumatol. 2017;36(11):2447-2453.
23. Chen X, Luo X, Wei Y, Sun H, Dai L, Tangzhou Y, et al. LncRNA H19 induces immune dysregulation of BMMSCs, at least partly, by inhibiting IL-2 production. 2021;27(1):61.
24. Yang J, Li Y, Wang L, Zhang Z, Li Z, Jia QJB. LncRNA H19 aggravates TNF-α-induced inflammatory injury via TAK1 pathway in MH7A cells. Biofactors. 2020;46(5):813-820.
25. Stuhlmüller B, Kunisch E, Franz J, Martinez-Gamboa L, Hernandez MM, Pruss A, et al. Detection of oncofetal h19 RNA in rheumatoid arthritis synovial tissue. Am J Pathol. 2003;163(3):901-11.
26. Wu J, Zhang T-P, Zhao Y-L, Li B-Z, Leng R-X, Pan H-F, et al. Decreased H19, GAS5, and linc0597 expression and association analysis of related gene polymorphisms in rheumatoid arthritis. 2019;10(1):55.
27. Wang H, Li J, Cheng Y, Yao JJGT, Biomarkers M. Association of long-chain noncoding RNA *H19* and *MEG3* gene polymorphisms and their interaction with risk of osteoarthritis in a Chinese Han population. 2020;24(6):328-337.
28. Song Y, Xing H, Zhou L, Zhang N, Yang MJAot. LncRNA H19 modulated by miR-146b-3p/miR-1539-mediated allelic regulation in transarterial chemoembolization of hepatocellular carcinoma. 2021;95(9):3063-3070.
29. Zaaber I, Mestiri S, Marmouch H, Tensaout BBHJJAE. Polymorphisms in TSHR gene and the risk and prognosis of autoimmune thyroid disease in Tunisian population. 2020;16(1):1-8.
30. Heidari Z, Salimi S, Rokni M, Rezaei M, Khalafi N, Shahroudi MJ, et al. Association of IL-1β, NLRP3, and COX-2 Gene Polymorphisms with Autoimmune Thyroid Disease Risk and Clinical Features in the Iranian Population. Biomed Res Int. 2021;2021:7729238.

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