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A PILOT STUDY SCOUTING THE ASSOCIATION OF HOTAIR GENETIC POLYMORPHISMS WITH GASTRIC CANCER RISK IN SOME EGYPTIAN PATIENTS

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ABSTRACT

Gastric cancer is one of the prevalent malignant tumors all over the world. In the current study we aimed at elucidating a possible correlation between LncRNA-HOTAIR polymorphisms rs7958904 G>C and rs874945 G>A and risk of developing gastric cancer in Egyptian patients. Blood samples were collected from controls and patients. We performed real-time polymerase chain reaction (RT-PCR) for genotyping of the two variant alleles at the SNPs sites of HOTAIR gene in all subjects. As regard rs7958904 SNP, there was statistically significant higher mutant genotype CC and Mutant C allele among gastric cancer patients and as regard rs874945 SNP, there was statistically significant higher mutant genotype AA and Mutant A allele among gastric cancer patients. As regard rs874945 SNP, the mutant genotype AA and the Mutant A allele were statistically significantly higher in Positive H. pylori patients than negative H. pylori patients. In Conclusion, the mutant genotypes (CC and AA) of rs7958904and rs874945 SNPs of LncRNA-HOTAIR gene predominate in gastric cancer patients that would displayed their impact in increasing the risk of developing gastric cancer in Egyptian patients, while the wild genotypes (GG and GG) predominate in controls which support our hypothesis.

Key words: HOTAIR, SNPs, RT-PCR.

INTRODUCTION

The occurrence and deaths from gastric cancer have decreased over the last 5 decades all over the world; however it considered the second main

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reason of cancer mortality in many areas of the world ***(Nagini, 2012)***. Unluckily, there are oftentimes no specified manifestations in the early stages of gastric cancer, and surgical intervention is often no longer a choice when diagnosed. Furthermore, therapeutic methods are restricted due to scarcity of information of the molecular and genetic standards of gastric carcinogenesis. Gastric cancer is a complicated process having several factors and steps which were attributed to various genetic and epigenetic variations ***(Wang et al., 2014).*** Many molecular and genetic agents have been utilized in gastric cancer studies encompassing non-coding RNAs (ncRNAs) ***(McLean and El-Omar, 2014).*** Multiple researches signalized that disturbed expression of lncRNA might be involved in numerous aspects of tumor, comprising pathogenesis, progression, and metastasis ***(Zhang et al., 2016).*** Lately, HOX transcript antisense intergenic RNA (HOTAIR) has been recognized as an oncogene. It has an important role in gene regulation and chromatin dynamics and seems to be constantly overexpressed in many types of malignant tumors. Increased expression of HOTAIR is related to tumor invasion, progression, distant metastasis, and poor prognosis of corresponding cancers ***(Wu et al., 2014).***

HOTAIR gene, a 2158 nucleotides in length long non coding RNA, is transcribed from the HOXC locus existed on chromosome 12q13.13 and plays a crucial role in gene regulation through changes in structure of chromatin (histone modifications) ***(Lv et al., 2013).*** Many researches displayed the effect of polymorphisms of HOTAIR gene on the occurrence of multiple cancers such as gastric cancer, ovarian cancer, prostate cancer, and breast cancer ***(Qiu et al., 2017, Taheri et al., 2017).*** Various single nucleotide polymorphisms (SNPs) in HOTAIR gene are frequently investigated in cancer susceptibility, progression, clinical consequences and response to treatment ***(Bayram et al., 2016)***. Lately, many studies have decidedly revealed the inconsistent and debatable associations of prevalent SNPs in HOTAIR gene (rs920778, rs1899663, rs7958904, rs874945, rs4759314, and rs12826786) with the incidence of different cancers as cancers of the digestive system ***(Pan et al., 2016, Jin et al., 2017).*** In the present study, we tried to elucidate a possible association of HOTAIR rs7958904 G>C and rs874945 G>A polymorphisms with gastric cancer development in a sample of Egyptian patients.

MATERIALS AND METHODS

This study was conducted on 50 participants; control group included 25healthy age and sex matching volunteers, 15 males and 10 females, aged 52.84 ± 4.15 years were selected from outpatient's clinics at El Fayoum University Hospital and gastric cancer group included 25 patients, 17 males and 8 females aged 54.28 ± 5.07 years were selected randomly from General Surgery Department, Fayoum University Hospital, Fayoum University, Egypt. All patients were subjected to full history taking, full clinical examination, and laboratory investigations. Histopthological diagnosis and staging of gastric cancer and were performed in accordance to standards instituted by ***Fenoglio-Preiser et al., 2000*** and the ***American Joint Committee on Cancer (AJCC) 2010 .*** We detected infection by H. pylori by Immunohistochemistry; sections were stained with hematoxylin and eosin (H&E), immunostaining with anti-H. pylori antibody (Dako, High Wycombe, UK) at a 1 in 1000 dilution utilizing a standard Streptavidin–biotin complex method was carried out **(Ashton-Key et al. 1996)**. Patients who received chemotherapy, radiotherapy or had any other malignant tumor were excluded from the study. Blood samples were collected before any surgeries or therapeutic interventions A written informed consent was provided by all participants of the study. All human studies have been reviewed and approved by Ethics Committee at Faculty of Medicine, Fayoum University. It was carried out in correspondence to the Ethical code of the World Medical Association (Helsinki's Declaration) for human-beings experimentations.

Sample Collection: 3 mL fresh venous blood of antecubital vein were collected from all participants by venipuncture into plain tubes containing ethylene-diamine-tetraacetic acid "EDTA" for assessment of Hemoglobin and DNA extraction. Another 3 ml venous blood samples were incubated at 37°C for 15 min. and centrifuged at 3000g for 10 min. to separate serum and stored in aliquots at −80°C. Serum was used to estimate alanine aminotransferase (ALT), aspartate aminotransferase (AST) and CEA. AST and ALT were estimated utilizing enzymatic colorimetric kits supplied by Biodiagnostics, Egypt. Hb was estimated by cell counter

(Sysmex XT-4000i Automated Hematology Analyzer, USA). CEA was estimated by an enzyme immunoassay kits, Fujirebio Diagnostics, Sweden.

DNA Extraction: The genomic DNA was extracted from whole peripheral blood sample using QIAamp DNA blood mini-kit extraction kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. All purified DNA samples were stored at 4°C until PCR application was performed.

Genotyping of rs7958904 (G/C) and rs874945 (G/A) polymorphisms of LncRNA HOTAIR.

The HOTAIR gene segments encompassing rs7958904 G>C in exon 6 and rs874945 G>A near 3′ region of the HOTAIR gene were amplified by RT-PCR with the TaqMan allelic discrimination assay (Applied Biosystems, Foster City, CA) utilizing the appropriate primers (Table 1). (***Wu et al., 2016***). The TaqMan® genotyping assay has 2 primers to amplify the concerning sequences and 2 TaqMan® minor groove-binding (MGB) probes for revealing alleles. These 2 probe-pairs in every reaction permits genotyping of the 2 predicted variant alleles at the SNPs of a target DNA. The genotyping screening marks the existence or lack of a SNP according to the fluorescence change in dyes connected with the probes. TaqMan® MGB probes comprised target-specific oligonucleotides with an appraiser dye at 5`-end of each probe: one VIC®-assorted probe to detect allele 1 sequence (G-allele of rs7958904 and G-allele of rs874945) and one FAM™-assorted probe to disclose allele 2 sequence (C-allele of rs7958904 and A-allele of rs874945). A fluorescence signal for both dyes indicates heterozygous for allele 1–allele 2. The 25 µl PCR mixture comprised 20 ng of extracted DNA from whole blood and: 0.5µl FAM and VIC probes and primers (Taqman SNP genotyping assays), 12.5 µl Taqman universal master mix II No UNG (Cat No. 4630080) and DNase free water. The PCR steps were: activation of enzyme for 10 minutes at 95 ºC, 40 cycles of 15 sec. for denaturizing DNA at 95 ºC, 20 sec. for annealing of primers and probes at 55 ºC and 30 sec. at 72 ºC for amplification. For interpretation of genotyping, we used StepOne Applied biosystem version 2.1 software analysis.

Statistical Analysis Data was assembled and coded to enable data handling and double-entered into Microsoft Access. Their analysis was done by SPSS software version 18 in windows 7. Plain descriptive analysis as numbers and percentages for qualitative data, standard

deviations as a measurement of dispersion for quantitative parametric data, and inferential statistic test: student t-test used to equiponderate measurements of 2 independent series of quantitative data. All HOTAIR polymorphisms in control group were in Hardy–Weinberg equilibrium. The level $P \leq 0.05$ was assessed the cut-off value for significance.

RESULTS

A total of 50 age and sex matched Egyptian subjects (25 healthy controls and 25 gastric cancer patients) were genotyped to elucidate a possible association of HOTAIR rs7958904 G>C and rs874945 G>A polymorphisms with gastric cancer susceptibility. Demographic and laboratory characteristics of all subjects are presented in **Table 1**. The genotype frequencies of 2 SNPs (i.e., rs7958904 and rs874945) among the controls were all in accordance with **HWE**. There was no statistically significant difference between controls and patients regarding age and sex **(Table 2).** There were statistically significant differences between controls and patients regarding Hemoglobin and CEA with low mean of Hemoglobin and high mean of CEA among patients **(Table 2).** Both mutant genotypes; **CC of rs7958904** SNP and **AA of rs874945** SNP were statistically significantly higher in gastric cancer patients(40% and 56% respectively) than controls (0% and 8% respectively), meanwhile, the wild genotypes **GG of rs7958904** SNP and **GG of rs874945** SNP were both statistically significantly higher in controls(60% and 60% respectively) than patients (24% and 24% respectively).

As regard rs7958904 G>C, The allelic frequencies of Gastric Cancer patients (G, 0.42; C, 0.58) were statistically significantly different from those of the healthy controls (G, 0.80; C, 0.20) (P = 0.006). As regard rs874945 G>A, The allelic frequencies of Gastric Cancer patients (G, 0.34; A, 0.66) were statistically significantly different from those of the healthy controls (G, 0.76; A, 0.24) (P = 0.009). As displayed in **Table 3**, a significant association between HOTAIR rs7958904 G>C polymorphism and risk of Gastric Cancer was detected in allele contrast and genetic models (G vs. C: OR = 2.5, 95% CI 1.45–4.49, P = 0.006; GG vs. GC+CC: OR = 1.9, 95% CI 1.12–3.22, P = 0.03; GG+GC vs. CC: OR = 6.1, 95% CI 1.02–44.52, P = <0.001). A significant association between HOTAIR rs874945 G>A polymorphism and risk of Gastric Cancer was detected in allele contrast and genetic models (G vs. A: OR = 2.6, 95% CI 1.54–4.34, P = 0.009; GG vs. GA+AA: OR = 1.9, 95% CI 1.12–3.22, P =

0.03; GG+GA vs. AA: OR = 5.3, 95% CI 1.77–27.66, P = 0.001). As regard **rs874945** SNP, the mutant genotype AA was statistically significantly higher in Positive H. pylori patients than negative H. pylori patients (77.8% and 43.8%, respectively) and the Mutant **A allele** was statistically significantly higher in Positive H. pylori patients than negative H. pylori patients (83.4% and 56.2%, respectively) **(Table 4)**. As regard rs7958904 SNP, the wild genotype GG was statistically significantly higher in stages I, II (38.5%) than stages III, IV (8.3%)). The mutant genotype CC was statistically significantly higher in stages III, IV (66.7%) than stages I, II (15.3%). As regard rs874945 SNP, the wild genotype GG was statistically significantly higher in stages III, IV (41.7%) than stages I,II (7.7%). The mutant genotype AA was statistically significantly higher in stages I, II (84.6%) than stages III, IV (25%).

Table (1): Primer sequences in HOTAIR gene polymorphisms.

Polymorphism	Primer sequence
rs7958904	Forward primer 1: 5`-CCGGACGTTCAACAATGGCATGTCC-3`
	Reverse primer 1: 5`-GCAAACTAATCTGGATTACGTAGT-C3`
rs874945	Forward primer 2: 5`-GTGAAACGCATCCCTATAGTATC-3`
	Reverse primer 2: 5`-GTAGAAATCCCTCCTGGGCTGACAC-3`

Table (2): Demographic and laboratory characteristics of patients.

Variable	Controls (N=25)	Gastric Cancer Patients (N=25)	P-value
Sex	**N (%)**		
Female	10 (40%)	8 (32%)	0.74
Male	15 (60%)	17(68%)	
	Mean ± SD		
Age	52.84 ± 4.15	54.28 ± 5.07	0.839
ALT(U/l)	24.75 ± 6.38	32.17 ± 4.00	0.04*
AST(U/l)	28.88 ± 7.01	31.92 ± 8.31	0.36
Hemoglobin (g/dl)	12.56 ± 1.44	10.40 ± 1.19	< 0.0001*
CEA(ng/ml)	2.32 ± 0.06	116.8 ± 14.32	< 0.0001*
H.pylori			
Positive	-	9 (36%)	
Negative	-	16(64%)	

TNM stage			
Stage I	-	7 (28%)	
Stage II	-	6 (24%)	
Stage III	-	8 (32%)	
Stage IV	-	4 (16%)	

***Significant at p-value ≤ 0.05** **ALT: Alanine aminotransferase**
AST: Aspartate aminotransferase **CEA: Carcinoembryonic antigen**

Table (3): Comparisons of HOTAIR SNPs genotypes in study groups.

Variable		Controls (N=25)	Gastric Cancer Patients (N=25)	OR (95% CI)	P-value[a]
rs7958904 G>C	**GG**	15(60%)	6 (24%)		**0.002***
	GC	10(40%)	9 (36%)		
	CC	0 (0.0%)	10(40%)		
	G allele	40(80%)	21(42%)	**1.00 (reference)**	**0.006***
	C allele	10(20%)	29(58%)	**2.5 (1.45–4.49)**	
	Dominant				
	GG	**15(60%)**	**6(24%)**	**1.00 (reference)**	**0.03***
	GC + CC	**10(40%)**	**19(76%)**	**1.9 (1.12–3.22)**	
	Recessive				
	GG + GC	**25(100%)**	**15(60%)**	**1.00 (reference)**	**<0.001***
	CC	**0 (0.0%)**	**10(40%)**	**6.1 (1.02–44.52)**	
rs874945 G>A	**GG**	15(60%)	6(24%)		**0.001***
	GA	8(32%)	5(20%)		
	AA	2(8%)	14(56%)		
	G allele	38(76%)	17(34%)	**1.00 (reference)**	**0.009***
	A allele	12(24%)	33(66%)	**2.6 (1.54–4.34)**	
	Dominant				
	GG	**15(60%)**	**6 (24%)**	**1.00 (reference)**	**0.03***
	GA + AA	**10(40%)**	**19 (76%)**	**1.9 (1.12–3.22)**	
	Recessive				
	GG + GA	**23(92%)**	**11(44%)**	**1.00 (reference)**	**0.001***
	AA	**2 (8%)**	**14(56%)**	**5.3 (1.77–27.66)**	

* Significant at p-value ≤ 0.05
[a] Data were calculated by logistic regression analysis

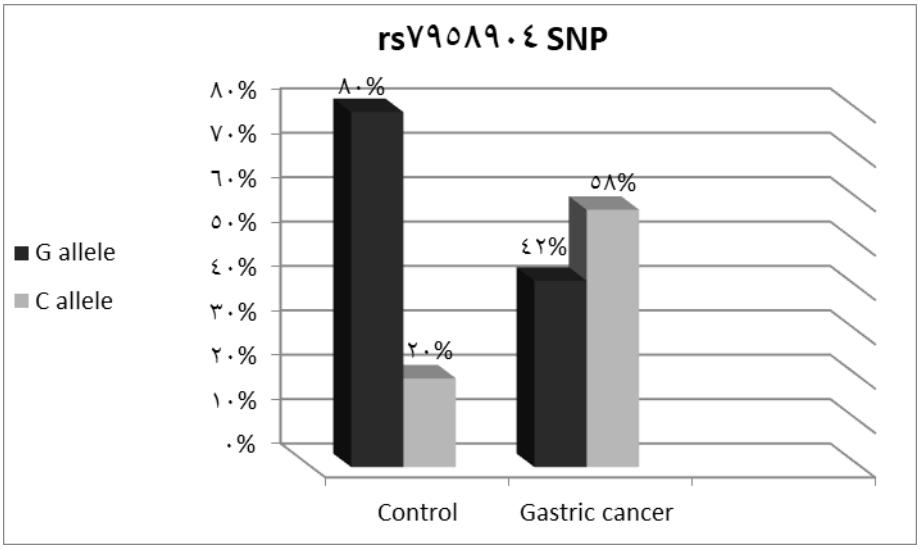

Figure (1): Allele frequency of rs7958904 SNP in the control and gastric cancer groups

Variable	Early stages (Stage I, II) (N=13)	Late stages (Stage III, IV) (N=12)	P-value

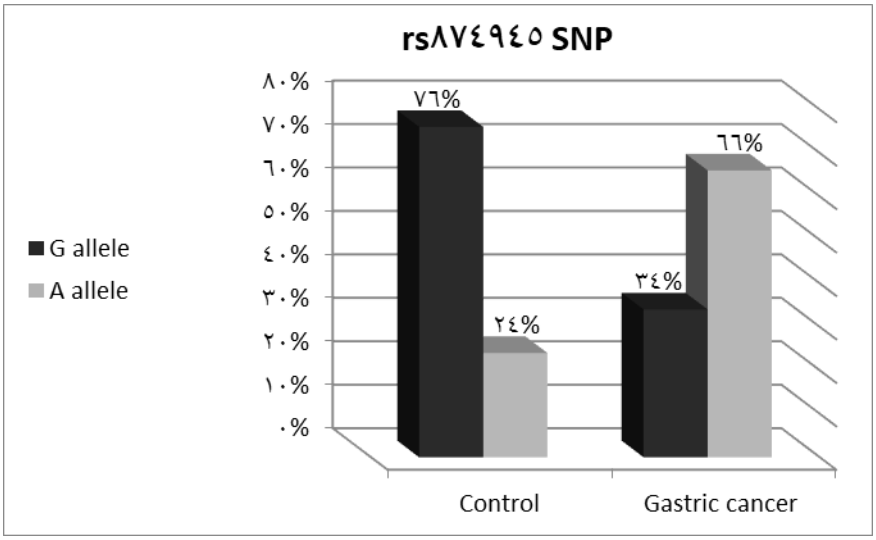

Figure (2): Allele frequency of rs874945 SNP in the control and gastric cancer groups

Table (4): Relation between HOTAIR SNPs genotypes and H. pylori infection.

*Significant at p-value ≤ 0.05

Table (5): Relation between HOTAIR SNPs genotypes and TNM staging

rs7958904 G>C	**GG**	5(38.5%)	1 (8.3%)	
	GC	6(46.2%)	3 (25%)	**0.01***
	CC	2(15.3%)	8 (66.7%)	
rs874945 G>A	**GG**	1(7.7%)	5(41.7%)	
	GA	1(7.7%)	4(33.3%)	**0.001***
	AA	11(84.6%)	3(25%)	

DISCUSSION

New advances in the genetic techniques had directed researchers to identify long non coding RNAs as novel biomarkers proposed particularly for their possible role in cancer progression **(Esteller, 2011).** Gastric cancer is one of the popular malignant tumors all over the world, so the insistence to find out novel biomarkers for diagnosis, monitoring, and prognosis evaluation of gastric cancer is of greatest significance for

Variable		Positive H. pylori(N=9)	Negative H. pylori (N=16)	P-value
rs7958904 G>C	**GG**	2(22.2%)	4 (25%)	
	GC	3(33.3%)	6 (37.5%)	**0.9**4
	CC	4(44.5%)	6 (37.5%)	
	G allele	7 (38.9%)	14(43.8%)	
	C allele	11 (61.1%)	18(56.2%)	
rs874945 G>A	**GG**	1(11.1%)	5(31.2%)	
	GA	1(11.1%)	4(25%)	**0.01***
	AA	7(77.8%)	7(43.8%)	
	G allele	3(16.6%)	14(43.8%)	
	A allele	15(83.4%)	18(56.2%)	

management of patients **(Hajjari et al., 2013).** HOTAIR is one of the utmost significant long non coding RNAs which is involved in multiple kinds of malignant tumors. It was reported that lncRNAs affected progression and metastasis of malignant tumors via chromosome remodeling, transcription and posttranscriptional modifications **(Cai et al., 2016).**

Liu et al., (2014) displayed that aberrant upregulation of HOTAIR acts as a good biomarker for poor prognosis of gastric cancer, and may give many attributes needed for tumor progression and metastatic phenotype. **Cai et al., (2014)** have identified that HOTAIR might act as an oncogene in

many types of cancers and its high expression could lead to malignant transformation of normal cells. Recently, studies demonstrating the association between polymorphisms in HOTAIR gene and the incidence of cancer in human have increased, however the explanation of the phenotypic impacts of these polymorphisms are convoluted and confounding denoting that the consequences which have revealed are confusing rather than decisive **(Zhang et al., 2014, Pan et al., 2016).** This study aimed to elucidate a possible correlation between LncRNA-HOTAIR polymorphisms rs7958904 G>C and rs874945 G>A and risk of developing gastric cancer in Egyptian patients. Regarding **rs7958904** and **rs874945** SNPs, our results displayed statistically significant higher mutant genotypes (CC and AA) among patients group (40% and 56%) than control group (0% and 8%) and statistically significant higher wild genotypes (GG and GG) among control group(60% and 60%) than patients group (24% and 24%) (P=0.002 and P=0.001, respectively). So the rs7958904 CC genotype and **rs874945** AA genotype were related to an increased risk of gastric cancer (OR = 6.1 and 5.3, respectively) compared with the GG/GC genotypes of rs7958904 and the GG/GA genotypes of **rs874945**.

Our results were in contrast with **Du et al**. **(2015)** who studied the association between 3SNPs of lncRNA HOTAIR (rs4759314, rs7958904 and rs874945) and gastric cancer risk in Chinese patients. They showed that rs4759314 SNP was significantly associated with the increased risk of gastric cancer [odds ratio (OR) of 1.39, P = 0.002] and observed that there was no significant association between both SNPs rs7958904 and rs874945 and gastric cancer risk.

We also found that the mutant C and A alleles of rs7958904 and rs874945 SNPs existed with a high percentage among gastric cancer patients (58% and 66%) compared to controls (20% and 24%). This would display their impact in the gastric cancer patients, affecting the encoded protein and consequently repressing the repairing mechanisms within the cells.

In our study we detected infection by H. pylori among gastric cancer patients and we found that 64% was Positive H. pylori. As regard **rs7958904** SNP, we found **no** statistically significant difference between different genotypes among positive and negative H. pylori patients (P=0.94). As regard **rs874945** SNP, we displayed that the mutant genotype AA was statistically significantly higher in Positive H. pylori

patients than negative H. pylori patients (77.8% and 43.8%, respectively) (P=0.01) and the Mutant **A allele** was statistically significantly higher in Positive H. pylori patients than negative H. pylori patients (83.4% and 56.2%, respectively).

Some studies displayed no significant association between H pylori and genotypes of HOTAIR gene SNPs among patients with gastric cancer **(Salek et al., 2015).** Others demonstrated that therapy used for eradication of H pylori could decrease the gastric cancer risk **(Fuccio et al., 2009),** while other researchers reported that gastric atrophy was associated with an elevated risk of gastric cancer and identified that there are potentially 2 kinds of gastric cardia adenocarcinoma, one related to gastric atrophy and infection of H pylori, and the other that looks like esophageal adenocarcinoma, on which gastric atrophy possesses no impact or even a preventative effect **(Islami et al., 2011).**

In the present study, we showed that the mutant genotype CC **of rs7958904** SNP was statistically significantly higher in stages III, IV (66.7%) than stages I, II (15.3%) while the mutant genotype AA of **rs874945** SNP was statistically significantly higher in stages I, II (84.6%) than stages III, IV (25%).

In conclusion, the mutant genotypes (CC and AA) of rs7958904and rs874945 SNPs of LncRNA-HOTAIR gene predominate in gastric cancer patients that would displayed their impact in increasing the risk of developing gastric cancer in Egyptian patients, while the wild genotypes (GG and GG) predominate in controls which support our hypothesis.

Limitations of study: limitation of our study was the small sample size, so further studies with larger sample size are needed to confirm our findings.

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المخلص العربى

دراسة العلاقة بين تعدد الاشكال الجينية rs7958904 و rs874945 في جين HOTAIR وخطر الاصابة بسرطان المعدة في المصريين

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يعتبر سرطان المعدة واحد من الأورام الخبيثة الشائعة في جميع أنحاء العالم. فى هذه الدراسة حاولنا دراسة العلاقة بين تعدد الاشكال الجينية rs7958904 و rs874945 في جين HOTAIR وخطر الاصابة بسرطان المعدة في المصريين.

لقد تم إجراء هذه الدراسه على ٢٥ شخص طبيعي كمجموعة تحكم و ٢٥ مريضا بسرطان المعدة.. أجرينا تفاعل البلمرة المتسلسل (RT-PCR) من أجل التنميط الجيني لتعدد الاشكال الجينية لجين HOTAIR في جميع افراد الدراسة.

لقد وجدنا ان الانماط الجينية الطافرة (CC و AA) والنسب المئوية للأليلات (C و A) زادت بشكل ذو دلالة احصائية فى مرضى سرطان المعدة والأنماط الوراثية الطبيعية (GG و GG) والنسب المئوية للأليلات (G و G) زادت بشكل ذو دلالة احصائية فى الاشخاص الطبيعية.

فيما يتعلق بالتعدد الجينى rs874945 ، كان النمط الوراثي الطافر AA و الأليل الطافر A عاليًا بشكل ذو دلالة احصائية في مرضى بكتيريا الهيليكوبكتر. فيما يتعلق بالتعدد الجينى rs7958904وجدنا ان النمط الجيني الطبيعي GG عاليًا بشكل ذو دلالة احصائية في المرحلتين الاولى والثانية عن المرحلتين الثالثة والرابعة و النمط الوراثي الطافر CC عاليًا بشكل ذو دلالة احصائية في المرحلتين الثالثة والرابعة عن المرحلتين الاولى والثانية.

فيما يتعلق بالتعدد الجينى rs874945 وجدنا ان النمط الجيني الطبيعي GG عاليًا بشكل ذو دلالة احصائية في المرحلتين الثالثة والرابعة عن المرحلتين الاولى والثانية و النمط الوراثي الطافر AA عاليًا بشكل ذو دلالة احصائية في المرحلتين الاولى والثانية عن المرحلتين الثالثة والرابعة.

الخلاصة ان تعدد الاشكال الجينية rs7958904 و rs874945 في جين HOTAIR قد يزيد من خطر الاصابة بسرطان المعدة في المصريين