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ORIGINAL ARTICLE

Case Control Study

Association between homeobox protein transcript antisense intergenic ribonucleic acid genetic polymorphisms and cholangiocarcinoma

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Author contributions: Lampropoulou DI and Laschos K performed the majority of the writing and were involved in the execution of the experiments; Gazouli M conceived the study, performed the majority of experiments, made critical revisions and writing; Papiris K, Aravantinos G, Georgiou K, Theodoropoulos G participated in the collection of the human samples and provided substantial contributions to the conception and design of the study; Filippou D made critical revisions and provided approval of the final version of the manuscript to be published.

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Abstract

BACKGROUND

Cholangiocarcinoma (CCA) represents a rare but highly aggressive malignancy that is often challenging to diagnose, especially in early stages. The role of existing tumor biomarkers for CCA diagnosis, remains controversial due to their low sensitivity and specificity. Increasing evidence has implicated long non-coding ribonucleic acid polymorphisms with cancer susceptibility in a variety of tumor types. The association between long non-coding ribonucleic acid homeobox protein transcript antisense intergenic ribonucleic acid (HOTAIR) polymorphisms and CCA risk has not been reported yet.

AIM

To investigate the influence of HOTAIR variants on the risk of CCA development.

METHODS

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We conducted a case-control study in which three HOTAIR single nucleotide polymorphisms (rs920778, rs4759314 and rs7958904) were genotyped in a Greek cohort. Our study population included 122 CCA patients (80 males and 42 females) and 165 healthy controls. The polymorphisms under investigation were examined in peripheral blood samples.

RESULTS

HOTAIR rs4759314 AG and GG genotypes were associated with a significantly increased CCA risk [P = 0.004, odds ratio: 3.13; 95% confidence interval: 1.65-5.91 and P = 0.005, odds ratio: 12.31; 95% confidence interval: 1.48-101.87, respectively]. However, no significant associations of HOTAIR rs920778, and rs7958904 were detected. Similarly, we found no significant associations between rs4759314 AA genotype and CCA susceptibility.

CONCLUSION

HOTAIR rs4759314 AG and GG genotypes may be implicated with CCA development and may serve as a potential diagnostic biomarker.

Key Words: Cholangiocarcinoma; Homeobox protein transcript antisense intergenic ribonucleic acid polymorphisms; Rs920778; Rs4759314; Rs7958904

Core Tip: The late-stage diagnosis and chemoresistance of cholangiocarcinoma has led to an urgent need to identify new diagnostic biomarkers for the early detection of this aggressive malignancy. Homeobox protein transcript antisense intergenic ribonucleic acid polymorphisms have emerged as potential diagnostic biomarkers for several types of cancers. We conducted a case-control study in order to investigate possible associations between three homeobox protein transcript antisense intergenic ribonucleic acid polymorphisms and risk for cholangiocarcinoma development.

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INTRODUCTION

Cholangiocarcinoma (CCA) represents an heterogenous group of highly aggressive, poor prognosis malignancies originating from the bile ducts[1]. Despite that surgical resection remains the best treatment option, late diagnosis often excludes patients with CCA from a potentially curative-intent primary resection[2]. However, even in cases of radical surgical approaches, a high risk of post-surgery recurrence exists. The presence of distance metastases confers even poorer prognosis decreasing further the 5-year-survival rates at 2%[3]. In advanced stages where surgical debulking offers no benefit or in cases with post-operative positive surgical resection margins, chemoradiation therapy enhances disease control and delays the rapid decline that characterizes CCA[4]. However, CCA is generally considered a chemotherapy-resistant malignancy displaying very low response rates to systemic therapy[5].

CCA diagnosis can be very challenging especially at an early stage; the suspicion arises usually from signs and symptoms associated with biliary obstruction, elevated levels of cholestatic liver enzymes and increased tumor markers such as carbohydrate antigen 19-9 and carcinoembryonic antigen. Moreover, several imaging techniques may be often indicative for the presence of bile mass or stricture. However, the role of tumor markers in CCA diagnosis remains controversial due to their low sensitivity and specificity[6]. Therefore, there is an urgent need to identify novel diagnostic and prognostic biomarkers as well as new therapeutic targets in order to improve the

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management of CCA patients.

Long-non coding ribonucleic acids (RNAs) belong to a large no protein-coding class of RNAs known as non-coding RNAs. The classification of non-coding RNAs is based on their length and includes several sybtypes such as microRNAs, long non-coding RNAs (lncRNAs) and circular RNAs. LncRNAs are more than 200 nucleotides long that play crucial roles in several pathophysiological conditions, including cancer[7]. Moreover, several studies have indicated that dysregulation of specific lncRNAs is associated with the development and promotion of different malignancies, including CCA[8].

Hox transcript antisense intergenic (HOTAIR) is lncRNA with distinct roles in multiple cancer-related processes such as cell proliferation, invasion, epithelial to mesenchymal transition and metastasis. Its overexpression has been corelated with the development and progression of several human cancers[9-12]. HOTAIR is a key regulator of gene expression at several levels (epigenetic, transcriptional and posttranscriptional). In terms of epigenetic modifications, HOTAIR regulates chromatin states by binding to the polycomb repressive complex 2[13]. For example, in breast cancer intergenic CpG island methylation has been associated with HOTAIR expression prognosis[11]. At a post-transcriptional level, HOTAIR can alter gene expression by binding to splicing factors or by interacting with transcription factors or ribosomes[14]. Chiyomaru *et al*[15] proposed that HOTAIR expression can be decreased by Argonaute2 complex in the presence of microRNA-141. Moreover, it has been suggested that the post-synthetic methylation of some HOTAIR cytosines may regulate HOTAIR function[16]. For instance, HOTAIR was found to increase the expression of the anti-apoptotic protein Bcl-w by sequestering miR-206 at the post-transcriptional level in breast cancer cells[17]. Furthermore, HOTAIR has been positively correlated with Hu antigen R which is a key regulator of posttranscriptional gene expression. Indeed, head and neck squamous cell carcinoma progression has been associated with the existence of a regulatory loop in which the expression of HOTAIR and Hu antigen R were mutually regulated[18]. Additionally, HOTAIR interference with siRNA was found to be associated with cell proliferation and prognosis in renal carcinoma cells[19] and endometrial cancer[20]. Similarly, HOTAIR appears to be upregulated in CCA tissue samples and cell lines and its overexpression was also correlated with tumor size, TNM stage, unfavorable prognosis and risk of post-surgery recurrence. Furthermore, it has been suggested that HOTAIR knockdown by siRNAs promoted cell apoptosis *in vitro* and decreased the migratory and invasion potential of CCA cells[21].

However, the underlying biological mechanism of HOTAIR in CCA was poorly investigated until very recently. Emerging evidence supports the role of lncRNAs in CCA progression *via* the competing endogenous RNA network[22]. Based on this, Lu *et al*[23] identified miR-204-5p as a target of HOTAIR and high mobility group B1 as a target of miR-204-5p. Ultimately, the authors proposed that this lncRNA acts as a competing endogenous RNA by sponging miR-204-5p and thus suppresses CCA cell apoptosis and autophagy and induces cell proliferation[23]. Moreover, a meta-analysis conducted by Min *et al*[24] in 2018 has associated HOTAIR polymorphisms with cancer development. Similarly, two updated recent meta-analyses concluded that several polymorphisms are indeed associated with cancer risk[25,26]. However, to the best of our knowledge HOTAIR polymorphisms and CCA risk have not been instigated, so far.

Based on the above, in the present study we aimed to investigate the possible associations between HOTAIR rs4759314, rs920778 and rs7958904 polymorphisms and risk for CCA development in a case-control study.

MATERIALS AND METHODS

Study population

A total of 122 CCA patients and 165 healthy individuals as controls were recruited in this study. The diagnosis of CCA was confirmed by histopathology. Healthy individuals were blood donors selected according to their physical examination and normal routine laboratory tests and have no history of any chronic diseases. The average age of CCA patients was 58 ± 8 (mean ± SD) years, with 80 males and 42 females, while the average age of healthy controls was 51 ± 10 years, with 108 males and 57 females. Among 122 CCA patients, 21 were intrahepatic CCA from surgical pathology findings. The study was approved by the University Hospital Ethical Committee and all patients gave their written informed consent regarding their participation.

Genotyping

Deoxyribonucleic acid was isolated from peripheral blood using the NucleoSpin Blood Kit (Macherey-Nagel, Germany) according to the manufacturer's instructions. HOTAIR single nucleotide polymorphism (SNP) rs920778 was genotyped using polymerase chain reaction (PCR)-restriction fragment length polymorphism as described previously[27]. For the rs4759314 we used an allele specific PCR analysis as previously described[28]. The rs7958904 polymorphism genotyping was determined using allele specific PCR. For rs7958904, the primers used were 5'-GGCCCGGTGTGG-GGCAGTGGCTGACCG-3' (G allele), 5'-GGCCCGGTGTGGGGCAGTGGCTGACCC-3' (C allele) and reverse 5'-GGCAGTTCCCGGAACAAACGTGGCAGAG-3'.

Statistical analysis

Genotype frequencies were compared with the chi-square with Yate's correction using Instat 3.0 package (GraphPad Software, San Diego, CA, United States). Odds ratios and 95% confidence intervals were obtained with Instat 3.0 package (GraphPad Software, San Diego, CA, United States). The *P* values are all two-sided, and *P* values of < 0.05 were significant. Hardy-Weinberg equilibrium was verified by calculating the expected frequencies and numbers and was tested separately in patients and in controls using the goodness-of-fit *Chi* square test.

RESULTS

As illustrated in Table 1, no significant associations were found between both HOTAIR rs920778 and rs7958904 genotypes and the study subpopulations (CCA patients *vs* healthy controls). However, a significant correlation was observed between carriers of rs4759314 GG genotype and risk for CCA development ($P = 0.005$). Our results indicated that the presence of the mutated G allele may be associated with increased risk for CCA development ($P < 0.0001$). Given the small number of intrahepatic CCA samples, no subgroup analyses were conducted. Moreover, we did not examine any possible correlations between the polymorphisms under investigation and several risk factors that have been associated with CCA pathogenesis, such as smoking, alcohol consumption or obesity, due to missing data.

DISCUSSION

CCA represents a highly aggressive tumor and includes three distinct subtypes (intrahepatic, perihilar and distal extrahepatic), based on the anatomic location[1]. The late-stage diagnosis and limited treatment options of CCA has led to an urgent need to identify new diagnostic biomarkers that can detect the disease in an early potentially curable stage. HOTAIR polymorphisms have been demonstrated to be involved with cancer development[24-26]. Over the last years, several studies have been conducted in order to detect possible associations between HOTAIR polymorphisms and cancer susceptibility; however, the results have been often controversial and inconsistent.

Previous studies have demonstrated that HOTAIR rs4759314 polymorphism plays an important role in the pathogenesis and progression of multiple diseases, including cancer[28-30]. Indeed, the results of a recent meta-analysis revealed that rs4759314 is included in the most common HOTAIR polymorphisms associated with cancer risk[25]. For instance, rs4759314 has been previously linked with HOTAIR overexpression in pancreatic cancer[31]. In line with Moazeni-Roodi *et al*[25] observations, another recent meta-analysis including more than 100 000 subjects, showed that rs4759314 HOTAIR may serve as a genetic cancer biomarker. More specifically, stratified analysis revealed that GG carriers of the HOTAIR rs4759314 had a significantly increased risk for pancreatic cancer than AA genotype. Additionally, the authors suggested that HOTAIR rs4759314 downregulates miR-545 and thus contributes to cancer development, *via* the promotion of cell proliferation and epidermal growth factor receptor *P*-extracellular signal-regulated kinase and *P*-P38 mitogen-activated protein kinase overexpression[26]. These observations are consistent with our findings which indicate that rs4759314 SNP is significantly correlated with CCA development. Furthermore, our results demonstrate that carriers of rs4759314 AG and GG alleles are in greater risk of CCA development. However, there are also several authors that have suggested no significant associations between rs4759314 and cancer susceptibility[32,33]. This inconsistency may be attributed to the extent of the studies, the heterogeneity of

Table 1 Single nucleotide polymorphism distribution

SNPs	Healthy controls (%)	CCA (%)	*P* value (OR; 95%CI)
rs920778			
TT	52 (31.51)	37 (30.33)	1
TC	83 (50.30)	61 (50)	1.00 (1.03; 0.56-1.760)
CC	30 (18.18)	24 (19.67)	0.86 (1.12; 0.57-2.22)
rs4759314			
AA	146 (88.48)	83 (68.03)	1
AG	18 (10.91)	32 (26.23)	0.0004 (3.13; 1.65-5.91)
GG	1 (0.61)	7 (5.74)	0.005 (12.31; 1.48-101.87)
rs7958904			
GG	89 (53.94)	71 (58.19)	1
GC	62 (37.57)	43 (35.25)	0.61 (0.87; 0.53-1.43)
CC	14 (8.48)	8 (6.56)	0.50 (0.72; 0.28-1.80)

SNPs: Single nucleotide polymorphisms; CCA: Cholangiocarcinoma; OR: Odds ratio; CI: Confidence interval.

genotyping methods and cancer types included in the meta-analyses. Further, stratified meta-analyses based on the type of malignancy and genotyping analysis, may be required in order to derive more reliable results.

With regards to HOTAIR rs920778 genetic variants and CCA risk, we found no significant correlations. Of note, subgroup analysis conducted in the two most recent meta-analyses, showed that the rs920778 was significantly associated with increased risk of gastrointestinal cancers[25,26]. Moreover, Liu *et al*[26] confirmed previous observations suggesting that since rs920778 is located in the enhancer region, it may be associated with HOTAIR overexpression and thus carcinogenesis promotion. Our findings are in line with Tian's *et al*[32] argument, who has also reported no significant associations between rs920778 HOTAIR polymorphisms and cancer risk. However, despite that our results did not demonstrate any direct correlations between HOTAIR rs920778 genotypes and CCA susceptibility, there is evidence that they are implicated with the development of other malignancies. For instance, the genotype combination of AG + TT (HOTAIR rs4759314 + rs920778) was found to differ significantly in rectal cancer patients[34]. Furthermore, significant associations have been reported between the HOTAIR rs920778 C>T polymorphism (TT *vs* CC genotypes) and hepatocellular carcinoma. More importantly, the authors suggested that the rs920778 TT genotype promoted significantly HOTAIR overexpression and induced cancer cell proliferation compared to the CC genotype in a Chinese population[35]. Similarly, rs920778 TT genotype has been also correlated with increased risk of esophageal squamous cell carcinoma, gastric cancer and papillary thyroid carcinoma[27,36,37].

Finally, our study revealed no significant associations between HOTAIR rs7958904 and CCA susceptibility. Our results are in line with the conclusions from recent meta-analyses that support no significant associations between increased cancer susceptibility and HOTAIR rs7958904 polymorphism[24-26]. However, several published results have been controversial regarding the possible role of this genetic polymorphism and cancer susceptibility. For example, Jin *et al*[38] have reported a possible association of rs7958904 CC genotype with increased cervical cancer risk compared to the GG/GC genotypes in a Chinese population. Moreover, in a hospital-based case-control study, the rs7958904 HOTAIR SNP was found to increase gastric cancer risk by 1.57-fold. Additionally, the authors reported a possible interaction between HOTAIR rs7958904 and HOTTIP rs1859168 polymorphisms that significantly increased gastric cancer risk[39]. Similarly, recently rs7958904 G>C has been associated with colorectal cancer prevalence and mortality[34], and CC rs7958904 genotype has been also linked with increased breast cancer risk compared to the GG homozygotes[40]. On the other hand, no significant associations were reported between increased risk for head and neck squamous cell carcinoma[29], whereas Li *et al*[33] concluded that rs7958904 decreases cancer risk, in a meta-analysis conducted in 2018.

Despite that the majority of our results are in line with the most recent meta-

analyses, several limitations exist in our study and thus our findings need to be treated with considerable caution. First of all, a more careful inspection of our study results, shows that the number of subjects that were hosts of rs4759314 AG and GG genotypes were very limited in both study groups (18 healthy controls *vs* 32 CCA patients and 1 healthy control *vs* 7 CCA patients, respectively). Secondly, several independent potential factors that may influence the results may have been ignored, such as gene-gene and gene-environment interactions. Therefore, our results need to be validated in future studies, so that larger CCA populations are included.

CONCLUSION

In summary, our study provides the first evidence of the potential association between carriers of HOTAIR rs4759314 AG and GG genotypes and CCA risk, suggesting that the presence of G allele HOTAIR rs4759314 of may serve as a diagnostic biomarker in CCA.

ARTICLE HIGHLIGHTS

Research background

The role of existing tumor biomarkers for cholangiocarcinoma (CCA) diagnosis, remains controversial due to their low sensitivity and specificity. Increasing evidence has implicated long non-coding ribonucleic acid (lncRNA) polymorphisms with cancer susceptibility in a variety of tumor types.

Research motivation

The association between lncRNA homeobox protein transcript antisense intergenic RNA (HOTAIR) polymorphisms and CCA risk has not been reported yet.

Research objectives

To investigate the role of lncRNA HOTAIR polymorphisms in CCA susceptibility.

Research methods

Case-control study on lncRNA HOTAIR genotypes.

Research results

HOTAIR rs4759314 AG and GG genotypes were associated with a significantly increased CCA risk [P = 0.004, odds ratio: 3.13; 95% confidence interval: 1.65-5.91 and P = 0.005, odds ratio: 12.31; 95% confidence interval: 1.48-101.87, respectively]. However, no significant associations of HOTAIR rs920778, and rs7958904 were detected. Similarly, we found no significant associations between rs4759314 AA genotype and CCA susceptibility.

Research conclusions

HOTAIR rs4759314 AG and GG genotypes may be implicated with CCA development and may serve as a potential diagnostic biomarker.

Research perspectives

To further investigate the biological role of HOTAIR on CCA pathogenesis.

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