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# Sex-specific association of the *rs4759314* polymorphism in the HOTAIR gene with urinary system cancer development

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**Abstract.** *The search for genetic markers of cancer remains one of the priority areas in oncology. Sex-specific genetic features of tumor development, particularly in urinary system tumors, are well documented.*
*The aim of this study was to investigate the possible association between the rs4759314 polymorphism of the long non-coding RNA HOTAIR gene and the development of urinary system cancers (USCs) in patients of different sexes.*
*Methods. Whole venous blood samples were obtained from 242 patients with USCs (101 patients with clear cell renal cell carcinoma [CCRCC] and 141 patients with transitional cell carcinoma of the urinary bladder [TCCUB]). Genotyping of the rs4759314 site of the HOTAIR gene was performed using real-time polymerase chain reaction (Real-time PCR) with the TaqMan assay C__27930754_10. Statistical analyses were conducted using Prism (version 10.4.1) and R (version 4.4.2) software.*
*Results. No significant differences were observed in the distribution of genotypes (AA, AG, GG) or alleles (A, G) for the rs4759314 polymorphism of the HOTAIR gene between patients with USCs and individuals in the control group ($P = 0.88871$, $\chi^2 = 0.02016$ for alleles; $P = 0.9788$, $\chi^2 = 0.0007095$ for genotypes). However, sex-specific differences in the distribution of HOTAIR gene allelic variants were identified. No overall association was found between the rs4759314 polymorphism and the development of USCs.*
*Conclusions. The distribution of rs4759314 polymorphic variants of the HOTAIR gene differs between male and female patients with USCs, with carriers of the minor allele being more common among women than among men ($P = 0.0105$).*
**Keywords:** *gene polymorphism; long non-coding RNA HOTAIR; clear cell renal cell carcinoma; transitional cell carcinoma of the urinary bladder.*

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**Єлізавета Строй**

# Статеві особливості зв'язку *rs4759314*-поліморфізму гена *HOTAIR* з розвитком раку сечовидільної системи

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**Резюме.** *Пошук генетичних маркерів онкологічних захворювань є одним із пріоритетних напрямів сучасної онкології. Відомі залежні від статі генетичні особливості розвитку пухлинного процесу, особливо пухлин сечовидільної системи.*

*Метою нашої роботи стало дослідження можливого зв'язку rs4759314-поліморфізму гена довгої некодуючої РНК HOTAIR з розвитком онкологічних захворювань сечовидільної системи у пацієнтів різної статі.*

*Методи. Для дослідження використано цільну венозну кров 242 осіб із раком сечовидільної системи (101 пацієнт зі світлоклітинним раком нирки та 141 хворий на перехідноклітинний рак сечового міхура). Генотипування за rs4759314-сайтом гена HOTAIR здійснювали методом полімеразної ланцюгової реакції у режимі реального часу (Real-time PCR) за наявності TaqMan assay C__27930754_10. Статистичну обробку отриманих результатів проводили за допомогою програм Prism (версія 10.4.1) та R (версія 4.4.2).*

*Результати. Встановлено, що не існує різниці у розподілі генотипів (AA, AG, GG) та алелів (A, G) за rs475931-поліморфізмом гена HOTAIR між хворими з онкологічними захворюваннями сечовидільної системи та особами контрольної групи ($P = 0,88871$, $\chi^2 = 0,02016$ для алелів, $P = 0,9788$, $\chi^2 = 0.0007095$ для генотипів). Показані статеві особливості розподілу алельних варіантів гена HOTAIR. Відсутній зв'язок між rs475931-поліморфізмом гена HOTAIR і розвитком онкологічних захворювань сечовидільної системи.*

*Висновки. Розподіл rs4759314-поліморфних варіантів гена HOTAIR відрізняється у осіб чоловічої і жіночої статей, хворих на онкологічні захворювання сечовидільної системи: серед жінок носії мінорного алеля зустрічаються частіше, ніж серед чоловіків ($P = 0,0105$).*

**Ключові слова:** *поліморфізм генів, довга некодуюча РНК HOTAIR, світлоклітинний рак нирки, перехідноклітинний рак сечового міхура.*

**Introduction.** Oncological diseases are a serious public health problem worldwide due to their high mortality rates, significant reduction in patients' quality of life, frequent disability of the working-age population, and the need for expensive and long-term treatment [1]. The renal cancer and the urinary bladder cancer are the most commonly diagnosed types of cancer in the urinary system. It is known that the development and prognosis of these cancers have significant sex-specific features. For instance, in the overall structure of human malignant diseases, renal cancer ranks 7th among men and 9th among women. Urinary bladder cancer is the eleventh most common cancer in the general population and ranks fourth in prevalence among men. Three-quarters of all urinary bladder cancer cases occur in men [2].

Many factors contribute to the onset and progression of cancer. However, in recent times, genetic predictors have been attracting increasing attention among scientists and doctors as influential risk factors for cancer development [3]. An undeniable and crucial role in carcinogenesis has been proven for long non-coding RNAs, including HOTAIR, which acts as a regulator of gene activity at the epigenetic and transcriptional levels [4 - 7]. The overexpression of HOTAIR in various types of cancer has led to its consideration as a candidate molecule for the diagnosis and treatment of oncological diseases [6].

Studies in this field are proceeding in two directions. The first direction is focused on studying the role of the long non-coding RNA HOTAIR in cancer development and metastasis. It has been shown that the overexpression of HOTAIR promotes the proliferation, migration, and invasion of CCRCC [8, 9]. It has been found that HOTAIR facilitates the metastasis of CCRCC by increasing the activity of histone H3K27 demethylase JMJD3 [10]. It has also been proven that patients with CCRCC who have a high level of HOTAIR expression have a significantly lower survival rate than patients with a low level of this RNA [11, 12].

The second direction is devoted to studying the role of polymorphic variants of the HOTAIR gene in the development of various types of cancer in different populations worldwide [13, 14]. It is known that the G allele of the HOTAIR rs4759314 polymorphism increases susceptibility to gastric cancer in the Chinese population [15, 16], while the rs1899663 polymorphism is a risk factor for the development of lung cancer [17]. A meta-analysis by Liu H. et al. investigated the association between the HOTAIR rs4759314 polymorphism

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and ovarian cancer [18]. Liu Y et al. demonstrated associations of the rs4759314, rs920778, and rs217717 polymorphisms with the development of cervical cancer in Chinese women [19]. Deng ZH et al. reported that the rs4759314 polymorphism influences the prognosis of prostate cancer in Chinese men [20]. In the study by Anber N. et al., no association was found between rs920778 polymorphic variants of HOTAIR and breast cancer in Egyptian women, whereas rs4759314 showed a statistically significant association with increased disease risk. Based on these findings, the authors suggested using this genetic marker in risk groups for prevention and early diagnosis [21]. In the population of Northeast China, the rs920778 and rs4759314 polymorphisms of the HOTAIR gene were significantly associated with susceptibility to breast cancer [22]. Similarly, associations of the rs12826786, rs920778, and rs4759314 variants of HOTAIR with breast cancer were reported in Mexican women [23]. The rs920778 polymorphism showed a significant positive association with breast cancer in Iranian women, while the rs12826786 and rs1899663 polymorphisms demonstrated negative associations in this population, and rs4759314 was not associated with disease risk [24].

Regarding kidney and bladder cancers, studies remain limited. It has been reported that the rs920778, rs4759314, and rs12427129 polymorphic variants of HOTAIR are associated with susceptibility to urothelial carcinoma in Taiwanese patients [25]. In contrast, the rs1899663 polymorphism of the HOTAIR gene was not associated with either the development of CCRCC [26] or patient survival in the Ukrainian population [27]. Sex-specific differences have been identified for the rs1899663 polymorphism: in heterozygous women, the risk of CCRCC development was higher than in homozygotes for either the dominant or minor allele [28]. No association was found between the rs1899663 polymorphism of the HOTAIR gene and either the occurrence or metastasis of TCCUB [29].

With respect to the rs4759314 polymorphism, data on its association with the development of urinary system cancers (USCs), as well as on sex-specific effects, are currently lacking. Therefore, the aim of our study was to investigate the potential association between rs4759314 polymorphic variants of the HOTAIR gene and the development of USCs in individuals of different sexes.

**Materials and methods.** *Study population.* The study included a cohort of 242 patients diagnosed with urinary system cancer (USC), comprising 101 individuals with clear cell renal cell carcinoma (CCRCC) and 141 with transitional cell carcinoma of the urinary bladder (TCCUB). A control group of 100 subjects without a history of oncological diseases of the urinary system was also enrolled. General clinical characteristics of the patients and control group individuals are presented in Table 1, while the characteristics of individuals of different sexes are shown in Table 2.

*Table 1*

**General clinical characteristics of patients with urinary system cancers**

| Indicator | Main group | Control group | P |
|---|---|---|---|
| Age, years | 65.1±11.8 | 77.38±8.499 | <0.0001 |
| Sex, f/m | 69/173 | 34/66 | 0.3143 |
| Smokers (%) | 119 (49.2) | 27 (27.0) | 0.0002 |
| Obesity (%) | 61 (25.2) | 18 (18.0) | 0.15 |
| Body weight, kg | 78.8±11.9 | 74.31±11.38 | 0.0015 |
| Height, cm | 171±7.6 | 165.8±10.26 | <0.0001 |
| BMI | 26.97±4.31 | 27.13±4.3 | 0.766 |
| Blood glucose, mmol/L | 55.1±15.8 | 52.68±7.905 | 0.14 |

Note: n – number of patients; f – female; m – male; P – statistical significance of differences. Categorical variables were compared using the $\chi^2$-test, and quantitative variables were compared using the t-test.

*Table 2*

**General clinical characteristics of patients with urinary system cancers by sex**

| Indicator | Female (%) | Male (%) | P |
|---|---|---|---|
| Age, years | 65.1±11.8 | 65.1±11.8 | 0.97 |
| Smokers (%) | 8 (11.6) | 111 (64.2) | <0.0001 |
| Alcohol consumption (%) | 26 (37.7) | 138 (79.8) | <0.0001 |
| Obesity (%) | 26 (37.7) | 35 (20.28) | 0.0048 |
| Body weight, kg | 76.4±14.2 | 79.8±10.8 | 0.05 |

*Продовження таблиці 1*

| Indicator | Female (%) | Male (%) | P |
|---|---|---|---|
| Height, cm | 165±5.78 | 174±6.72 | <0.0001 |
| BMI | 28.14±5.19 | 26.51±3.82 | 0.008 |
| Blood glucose, mmol/L | 55.3±16.7 | 55.1±15.5 | 0.89 |
| Diabetes (%) | 13 (18.8) | 40 (23.1) | 0.47 |
| Arterial hypertension (%) | 43 (62.3) | 98 (56.6) | 0.42 |

Note: n – number of patients; f – female; m – male; P – statistical significance of differences. Categorical variables were compared using the $\chi^2$-test, and quantitative variables were compared using the t-test.

All cancer patients were managed and diagnosed at the Sumy Regional Clinical Oncology Center between March 2011 and May 2020. Following radical tumor excision, histological analysis confirmed the diagnosis for each patient. All cases were clinically staged as II according to the TNM Classification of Malignant Tumors. The final morphological diagnosis adhered to the guidelines provided by the European Association of Urology [30]. Subjects with concurrent tumors at other sites, known hereditary disorders, or conditions of unestablished etiology were not included in the study.

*Genotyping.* To investigate the rs475931 polymorphism of the HOTAIR gene, venous blood samples were aseptically collected. Each sample was placed in a 2.7 ml monovette containing potassium ethylenediaminetetraacetic acid (11.7 mM) as an anticoagulant (Sarstedt, Germany). The blood specimens were subsequently frozen and stored at -20°C. DNA was isolated from whole blood leukocytes using a GeneJET Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific, USA). Genotyping of the rs475931 polymorphic site was carried out at the Scientific Laboratory of Molecular Genetic Research at Sumy State University via real-time polymerase chain reaction (Real-time PCR), utilizing a QuantStudio 5 DX Real-Time instrument (Applied Biosystems, USA). The analysis employed TaqMan assays (TaqMan®SNP Assay C__27930754_10; Catalog number: 4351379) and a PCR Real-Time reagent kit (Thermo Fisher Scientific, USA). The amplification process involved an initial denaturation phase at 95°C for 10 minutes, followed by 45 cycles, each consisting of a 15-second step at 95°C and a 30-second step at 60°C. Data curves were analyzed using the software provided with the QuantStudio 5 DX Real-Time system.

*Statistical analysis.* The statistical evaluation of the results was conducted using Prism software (version 10.4.1) and R (version 4.4.2). The genotype distribution was assessed for conformity with Hardy-Weinberg equilibrium using the online tool Equilibrium WpCalc (https://wpcalc.com/en/equilibrium-hardy-weinberg/). The distribution of rs475931 genotypes across the groups was analyzed with Pearson's $\chi^2$ test, and mean values were compared using a two-tailed Student's t-test. The risk of developing urinary tract cancer in relation to the rs475931 polymorphism of the HOTAIR gene was determined via logistic regression, employing a dominant inheritance model (AA vs. AG+GG). To account for potential confounders, including patient sex, age, body mass index (BMI), and smoking habits, a multivariable logistic regression analysis was performed. Statistical significance was defined as a P-value < 0.05, with all tests being two-tailed.

**Results.** In the conducted studies, the distribution of rs4759314 genotypes and alleles of the HOTAIR gene was analyzed in patients with USC (main group) and control group individuals (Table 3).

*Table 3*

**Frequency of alleles and genotypes for the rs4759314 polymorphism of the HOTAIR gene in the compared groups**

| Indicator | Main group | | Control group | | P ($\chi^2$) |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Genotypes | | | | | |
| AA | 220 | 90,9 | 91 | 91 | 0.978 (0.0007) |
| AG + GG | 22 | 9.1 | 9 | 9 | |
| Alleles | | | | | |
| A | 461 | 95.2 | 191 | 95.5 | 0.888 (0.021) |
| G | 23 | 4.8 | 9 | 4.5 | |

Note: n – number of patients; $\chi^2$ and P reflect the differences in distribution between the compared groups.

It was found that there were no differences in the distribution of the major and minor alleles between the compared groups: A = 461 (95.2%), G = 23 (4.8%) in the main group and A = 191 (95.5%), G = 9 (4.5%) in the control group (P = 0.88871; $\chi^2$ = 0.02016). The genotype distribution for the studied polymorphism in the main group was as follows: AA – 220 (90.9%), AG + GG – 22 (9.1%); in the control group, it was 91 (91%) and 9 (9%), respectively. The P-value, calculated using Pearson's $\chi^2$-test, was 0.9788, indicating no difference in genotype distribution between patients with USC and the control group individuals.

The next step of the analysis was to study the sex-specific features of the association between the rs4759314 polymorphism of the HOTAIR gene and the development of USC. Table 4 presents data on the frequency of genotypes for the rs4759314 locus of the HOTAIR gene in male and female patients of the main and control groups (Table 4).

*Table 4*

**Frequency of alleles and genotypes for the rs4759314 polymorphism of the HOTAIR gene in the compared groups by sex**

| Group | Genotypes | | | | $P_1$ ($\chi^2$) |
|---|---|---|---|---|---|
| | AA | | AG+GG | | |
| | n | % | N | % | |
| Men | | | | | |
| Main group | 166 | 95,9 | 7 | 4,1 | 0,5064 (0,4415) |
| Control group | 62 | 93,9 | 4 | 6,1 | |
| Women | | | | | |
| Main group | 54 | 78,3 | 15 | 21,7 | 0,3961 (0,7201) |
| Control group | 29 | 85,3 | 5 | 14,7 | |
| P2 ($\chi^2$) =0,0105 (18,68); P3 ($\chi^2$) = 0,152 (2,048) | | | | | |

Note: n – number of patients; P1 – indicator of the significance of differences between patients with genitourinary system cancers and controls; P2 – indicator of the significance of differences between patients of different sexes; P3 – indicator of the significance of differences between individuals of the control group of different sexes (Pearson's $\chi^2$-test).

Thus, among male patients with USC, the genotype distribution was as follows: AA – 166 (95.9%), AG + GG – 7 (4.1%), while in men of the control group, it was AA – 62 (93.9%) and AG + GG – 4 (6.1%), respectively (P = 0.5064).

In the female group, the ratio of homozygotes for the major allele (AA) to carriers of the minor allele (AG + GG) was 54 (78.3%) to 15 (21.7%) among patients with USC, and 29 (85.3%) to 5 (14.7%) among female individuals in the control group. No significant differences in genotype distribution were found between control group individuals of different sexes (P = 0.3961).

The association between the rs4759314 polymorphism of the HOTAIR gene and USC was analyzed using binary and multivariable logistic regression (Table 5).

*Table 5*

**Analysis of the association between the rs4759314 polymorphism of the HOTAIR gene and the development of urinary system cancers in individuals of different sexes according to the dominant inheritance model**

| Group | $P_c$ | ORc (97,5% CI) | $P_a$ | ORa (97,5% CI) |
|---|---|---|---|---|
| Men + women | 0,98 | 1,01 (0,45 – 2,28) | 0,94 | 1,04 (0,39 – 2,77) |
| Men | 0,51 | 0,65 (0,18 – 2,31) | 0,32 | 0,45 (0,095 – 2,15) |
| Women | 0,40 | 1,61 (0,53 – 4,88) | 0,30 | 1,98 (0,53 – 7,33) |

Note: 97,5% CI – confidence interval; Pc – crude P value (without adjusting for covariates); ORc – crude odds ratio; Pa – P value adjusted for age, smoking status and body mass index; ORa – adjusted odds ratio.

According to the dominant inheritance model, no such association was found, either for the overall main group (P = 0.98) or separately for men (P = 0.51) and women (P = 0.40). After adjusting for age, sex, smoking habits, and BMI, the association did not appear (P = 0.94 for the main group, P = 0.32 for men, P = 0.30 for women).

**Discussion.** Long non-coding RNAs (lncRNAs) are a class of RNA transcripts longer than 200 nucleotides that typically do not code for proteins or peptides [13]. Recent studies have shown that the dysregulation of lncRNA expression profiles is widely involved in the pathogenesis of tumors, including cell proliferation, migration, invasion, epithelial-mesenchymal transition,

apoptosis, and resistance to anti-tumor drugs [31]. One of the first lncRNAs whose role in cancer pathogenesis was demonstrated was HOTAIR [32]. Numerous studies have provided evidence that HOTAIR can promote the development of CCRCC through various mechanisms [33]. Increased HOTAIR expression stimulates the growth and invasion of CCRCC cell lines. HOTAIR is also a key factor in renal cancer metastasis. According to Katayama et al., HOTAIR regulates insulin-like growth factor-binding protein 2, which enhances the migration of renal cancer cells and is closely associated with metastasis to the lungs and lymph nodes, as well as influencing the nuclear grade in renal cancer [34]. The research by Gholami N. et al. revealed that HOTAIR stimulates tumor angiogenesis through an interaction with the androgen receptor [35].

The HOTAIR gene is located within the Homeobox C (HOXC) gene cluster on chromosome 12 and is co-expressed with the HOXC genes. It functions through an RNA product, which binds lysine-specific demethylase 1 (LSD1) and Polycomb repressive complex 2 (PRC2), and serves as a scaffold to assemble these regulators at the HOXD gene cluster, thereby promoting epigenetic repression of HOXD [13].

The HOTAIR gene consists of 6 exons and 5 introns. As of June 2025, this gene contains 6,794 single nucleotide polymorphisms (SNPs) (https://www.ncbi.nlm.nih.gov/snp/?term=HOTAIR+homo+sapiens). The rs4759314 polymorphism is located at position 53,968,051 and is a highly variable marker, as all four types of nucleotides (G, A, C, T) can occur at this locus (https://www.ncbi.nlm.nih.gov/snp/rs4759314). The rs4759314 polymorphism is located in an intron and may confer different promoter activity depending on the present nucleotide, which leads to varying expression levels of the HOTAIR gene [13].

The available data on the influence of polymorphic variants of the rs4759314 HOTAIR gene on USC are limited and contradictory. In our study, we analyzed the association of rs4759314 polymorphic variants with the development of USC (CCRCC and TCCUB). We showed that in the Ukrainian population there was no significant difference in the distribution of genotypes (AA, AG, GG) and alleles (A, G) between patients with USC and individuals in the control group. Furthermore, no association was found between the rs4759314 polymorphism of the HOTAIR gene and the risk of developing USC.

Krishna BM et al. demonstrated a correlation between HOTAIR rs4759314 and the development of cancer (without localization-based subdivision). Scientists have proven that the relationship was observed in the Asian population but absent in the Iranian one [4]. Akkoç Y did not find a link between the rs4759314 polymorphism of the HOTAIR gene and the development of bladder cancer in a European population. The authors explain this result by the insufficient number of patients (98 people) and plan to expand their research [36]. As our studies show, there is no association between the rs4759314 polymorphic variants and the development of USC in the Ukrainian population. Regarding other types of cancer, such studies concerning this genetic marker are currently absent in Ukraine.

Additionally, our work examined the features of genotype distribution in USC patients of different sexes. We have shown that the ratio of rs4759314 allelic variants of the HOTAIR gene differs in female and male patients: carriers of the minor C allele are found more frequently in women than in men. The study by Tung et al. found that in women with urothelial carcinoma, the rs4759314 polymorphism of the HOTAIR gene is associated with a higher probability of tumor development and a worse prognosis [25]. Other studies on sex-specific features of genetic distribution for the rs4759314 polymorphism of HOTAIR in patients with USC are lacking both in the Ukrainian population and other populations. Regarding other polymorphisms, a sex-dependent association of the rs1899663 polymorphism of the HOTAIR gene with the development of CCRCC has been demonstrated: in heterozygous women, the risk of developing the disease is higher than in homozygotes for the dominant or minor allele [28].

*Study limitations.* A limitation of our study was the lack of analysis of the dependence of HOTAIR gene expression on the rs4759314 polymorphic site. The relatively small sample size for analysis can also be considered a limitation. Perhaps an increase in the number of patients with USC, together with a functional analysis of the rs4759314 polymorphism, will allow a final conclusion to be drawn about the possibility of using this genetic factor as a diagnostic marker for the development of USC. Alongside this, it should be noted that this study is the first to search for sex-specific features of the association of HOTAIR genetic polymorphism with the development of USC both in Ukraine and worldwide.

**Conclusions:**

1. There is no difference in the distribution of genotypes (AA, AG, GG) and alleles (A, G) between patients with USC and individuals in the control group for the rs475931 polymorphism of the HOTAIR gene.
2. No association was found between the rs475931 polymorphism of the HOTAIR gene and the development of USC.
3. The ratio of rs4759314 allelic variants of the HOTAIR gene differs in groups of men and women with urinary system cancer: in female subjects, carriers of the minor allele are found more frequently than among men ($P = 0.0105$).

**Ethical declaration.** The research protocol received approval from the Ethics Committee of the Educational and Scientific Medical Institute at Sumy State University (protocol no. 5/07.2022) and was conducted in line with the principles outlined in the Declaration of Helsinki. All participants provided informed written consent before their personal data was processed and blood samples were collected for genetic analysis.

**Conflict of interest.** The author declares no conflict of interest.

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**Author contributions.** Yelizaveta Stroy was solely responsible for the conception and design of the study, genetic testing, data analysis and interpretation, drafting of the manuscript, and approval of the final version for publication.

**Data availability statement.** The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

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