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LONG NON-CODING RNA SNHG1 AS A DIAGNOSTIC AND PROGNOSTIC MARKER OF BLADDER CANCER

Abstract

Bladder cancer (BC) is one of the most prevalent cancers globally, and it ranks as the fifth most common malignancy among men in Ukraine. Modern diagnostic tools for bladder cancer have significant limitations: some of them are overly invasive and others lack sufficient sensitivity and specificity. Currently, molecular markers are becoming a promising tool for identification of oncogenic processes. Among epigenetic mechanisms involved in malignant cell transformation, long non-coding RNA (lncRNA)s are of particular interest, as they can act as either oncogenes or tumor suppressors. Available studies suggest that the lncRNA SNHG1, which is currently understudied, promotes tumor proliferation and inhibits apoptosis in malignant cells. The aim of the current study was to analyze changes in the relative expression of SNHG1 in tumor tissues and its levels in cell-free urine of bladder cancer patients, and to evaluate its diagnostic and prognostic value. There was a statistically significant increase in the SNHG1 gene expression level in tumor tissues compared to conditionally normal tissues. Also, a significant decrease in relative levels of SNHG1 transcripts was observed in urine of BC patients compared to healthy individuals. According to the analysis of ROC curves analysis, the chosen marker can identify bladder cancer with high sensitivity and specificity. A positive correlation was also discovered between SNHG1 expression level in tumor tissue and cancer stage. The obtained data support the relevance of further study on lncRNA SNHG1 as a promising diagnostic and prognostic marker of bladder cancer.

Keywords: bladder cancer, epigenetic biomarkers, lncRNA, SNHG1, tumor tissues, liquid biopsy.

Introduction

Bladder cancer (BC) is one of the most prevalent malignancies worldwide. According to the World Health Organization, in 2022 bladder cancer ranked 9th in the world in terms of incidence (614,298 cases) and 13th in terms of cancer-related mortality (220,596 deaths). In Ukraine, bladder cancer is the fifth most common oncological disease among men. Globally, more than three-quarters of bladder cancer cases occur in males [1]. The majority of BC cases are associated with a family history of cancer as well as external risk factors, including tobacco smoking, occupational exposure (such as work in the aluminum and rubber production or with dyes and dye intermediates), ionizing radiation, and chronic *Schistosoma haematobium* infection [2].

The most common type of bladder cancer is urothelial carcinoma, which accounts for over 90% of cases. The remaining 10% include squamous cell carcinoma and adenocarcinoma [3]. In many patients, bladder cancer is detected at an early, non-muscle-invasive stage, when the cancer has not yet spread into the muscular layer of the bladder wall. These tumors typically present with *FGFR3* gene

mutations and chromosome 9 aberrations. On the other hand, flat carcinomas *in situ* often progress to muscle-invasive type, and are commonly associated with *TP53* mutations, chromosome 9 deletions, and DNA hypermethylation [4].

The most widely used diagnostic tools for bladder cancer are white-light cystoscopy and urine cytology. However, both methods present significant limitations, including low sensitivity and specificity [5]. Regular monitoring of the disease requires non-invasive diagnostic methods that can be safely and frequently repeated. The increasing amount of research on the molecular mechanisms of bladder cancer offers opportunities for frequent, non-invasive check-ups, contributing to more accurate and effective diagnostics. One of the promising new approaches is liquid biopsy – the analysis of biological fluids, particularly blood and urine, for molecular indicators of different pathologies [6].

Epigenetic mechanisms, including DNA methylation and non-coding RNAs, are known to be involved in gene expression regulation. Thus, malignant transformation may result not only from the presence of mutant alleles of certain genes, but also from dysregulation of normal (wild-type) alleles due to abnormalities in epigenetic regulatory mechanisms. In late-stage, high-grade muscle-invasive tumors, serious alterations in DNA methylation are observed, along with changes in the activity of non-coding RNAs [7]. Currently, epigenomic modifications are being investigated both as potential biomarkers and as therapeutic targets [8]. For example, data on aberrant promoter methylation patterns allow the development of diagnostic panels that include genes encoding growth factors (*GDF15*), intermediate filament proteins (*VIM*), transmembrane proteins (*TMEFF2*), transferases (*MYO3A*), and carbonic anhydrases (*CA10*) [9-11].

More recently, there has been increasing evidence of the crucial role of long non-coding RNAs (lncRNAs) in oncogenesis. Dysregulation of lncRNA has been associated with cell migration, invasion, metastasis, and transcriptional abnormalities [12]. Several lncRNAs, such as GAS6-AS2, PTENP1 and H19, participate in the epithelial-mesenchymal transition and may serve as potential diagnostic and prognostic biomarkers [13].

Some lncRNAs are suggested to function as tumor suppressors. For instance, GAS5 has been shown to inhibit tumorigenesis by regulating the Wnt/β-catenin signaling pathway. In bladder cancer tissues, GAS5 silencing has been reported, which correlates with tumor stage, grade, and metastasis [14].

Our previous research on epigenetic markers of cancer investigated alterations in gene methylation and lncRNA expression during oncogenesis. The goal was to assess the potential of these changes as biomarkers for bladder cancer. A statistically significant increase in the expression of the RASSF1A splice variant of the protein-coding gene *RASSF1* was detected in tumor tissues, while a significant decrease in the relative quantity of both RASSF1A and its antisense lncRNA ANRASSF1 transcripts was observed in urine samples [18]. These findings highlight the need for further identification of lncRNAs with altered expression in oncogenesis to develop diagnostic panels that possess high sensitivity and specificity.

SNHG1 gene (Small Nucleolar RNA Host Gene 1) is located on chromosome 11 and belongs to the *SNHG* gene family, which encodes lncRNAs involved in essential cellular processes. SNHG1 has been identified as a key regulatory RNA in different diseases. For example, a positive feedback loop between SNHG1 and the transcription factor c-Myc promotes cardiac muscle regeneration after myocardial infarction, while in epilepsy, SNHG1 modulation of the miR-181a/BCL-2 axis delays disease progression. Dysregulated SNHG1 expression has been reported in multiple cancer types, including breast, prostate, gastric, colorectal cancer, osteosarcoma, and acute myeloid leukemia [15].

In bladder cancer, SNHG1 promotes tumor cell proliferation and inhibits apoptosis. Significantly elevated expression levels of *SNHG1* were observed both in patient tissue samples and *in vitro* cell cultures. High *SNHG1* expression is associated with poor BC prognosis [16,17]. Even though *SNHG1* expression has been studied in tissue samples, its presence and quantity in urine of bladder cancer patients compared to healthy individuals have not yet been investigated. Analysis of SNHG1 levels in urine represents a non-invasive diagnostic approach and offers great potential for improving bladder cancer detection and monitoring disease progression. Thus, the aim of this study was to identify changes in relative expression of *SNHG1* in tumor tissues and relative levels of its transcript in urine samples of BC patients and evaluate the potential of SNHG1 as a molecular marker of bladder cancer.

Materials and methods

All the samples and patient clinical data were obtained at the National Cancer Institute of the Ministry of Health of Ukraine between November 2018 and July 2022. To obtain compelling results, it was decided to collect both tissue and urine samples. Tumor tissues as well as paired conditionally normal tissues were obtained during surgeries of patients previously diagnosed with bladder cancer.

Urine samples of the patients were collected immediately before surgery. Urine of healthy individuals was used as control. There is a partial overlap between tissue and urine samples, since we were able to obtain both sample types from some patients and only one of those from others.

Table 1

Sizes of the samples used in the study

Sample type	Sample count
Tumor tissues	19
Conditionally normal tissues	19
Urine of patients	24
Urine of healthy individuals	15

Sizes of the samples used in the study

All samples were collected with informed consent following the Declaration of Helsinki and guidelines issued by the National Cancer Institute of Ukraine and the Ethics Committee of Institute of Molecular Biology and Genetics of the National Academy of Sciences of Ukraine. Patient clinical data used in correlation analysis is presented in an encrypted form.

Tissue samples obtained during surgery were immediately frozen in liquid nitrogen and stored at -80 °C until the next step of the research. Urine was stored in sterile containers at 2–8 °C. Before RNA extraction, tissue samples were homogenized using additional liquid nitrogen and a mortar and pestle. Urine samples were centrifuged for 15 min at 4 °C and 1500 g to precipitate epithelial cells. After that, supernatant was transferred into clean tubes to obtain cell-free urine. RNA was extracted using TRIzol reagent (ThermoFisher Scientific, USA) according to the manufacturer's protocol. To evaluate RNA concentration and purity, received samples were analyzed with NanoDrop 2000 (Thermo Fisher Scientific, USA).

cDNA synthesis on RNA template was performed with Maxima First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, USA). Afterwards, DNA samples were amplified during qPCR using HOT FIREPol EvaGreen qPCR Mix (Solis BioDyne, Estonia) according to manufacturer's protocol and a CFX96 Real-Time PCR Detection System with CFX Manager software (BioRad, USA). Primer sequences for the reaction were:

F. *ACTB* 5'TGACGTGGACATCCGCAAAG3'

R. *ACTB* 5'CTGGAAGGTGGACAGCGAGG3'

F. *SNHG1* 5'TAACCTGCTTGGCTCAAAGGG3'

R. *SNHG1* 5'CAGCCTGGAGTGAACACAGA3'

Conditions for qPCR were as follows: initial denaturation at 95 °C for 12 min; 41 cycle of denaturation at 95 °C for 15 sec, annealing at 60 °C for 20 sec, extension at 70 °C for 15 sec; final extension at 65 °C for 5 sec; finishing step at 95 °C for 30 sec. A plate read was performed after every amplification cycle.

qPCR products were separated in 0,8% agarose gel to confirm amplification specificity and primer quality. From the raw data obtained from qPCR, *SNHG1* relative expression levels were calculated. *Actin beta* was used as a reference gene, as its expression level doesn't change during oncogenesis. Calculations were carried out according to the formula

$$RQ = 2^{\Delta Ct},$$

RQ – relative quantity of amplification product; $\Delta Ct = Ct_{ACTB} - Ct_{SNHG1}$; Ct – number of amplification cycles needed for reaching fluorescence threshold.

Statistical analysis was performed in GraphPad Prism 8.4.3 application (https://www.graphpad.com/). SNHG1 relative quantity data was checked for outliers using an interquartile range method. To check the samples for normality, Shapiro-Wilk test was used (appropriate for sample count ≤ 30). Since tissue samples showed a Gaussian distribution, we used a parametric test – Student's *t*-test – for a pairwise comparison of *SNHG1* relative expression levels in tumor and conditionally normal tissues. A non-parametric Mann–Whitney test was used to compare data on SNHG1 relative quantities in urine of bladder cancer patients and control group of healthy individuals.

The diagnostic value of SNHG1 as BC biomarker was assessed with ROC curve method [19,20]. Correlation analysis of the gene relative expression levels and patients' clinical data was performed using Spearman rank correlation method. Finally, we used ANOVA to compare expression levels of patients grouped by cancer stage.

Results and discussion

We used qPCR to assess the relative quantity of *SNHG1* transcripts in biological material obtained from BC patients and healthy individuals via real-time PCR. The primary data represent the cycle threshold values, i.e. the number of amplification cycles needed to reach the fluorescence detection threshold. These Ct values were used to calculate the relative expression level of *SNHG1* in tissue and urine samples, using the *β-actin* gene as the reference gene.

To exclude extremely high or low values that may have resulted from experimental error, outlier detection was performed using the interquartile range method. Outliers identified among tissue samples were removed from the dataset together with the paired value from the parallel group to

Table 2

Sample sizes and normality test results for tissue and urine

Sample type	Sample count	Shapiro-Wilk test statistic	Test result
SNHG1 T	13	0,9436	*
SNHG1 N	13	0,9577	*
SNHG1 C	16	0,4987	**
SNHG1 H	5	0,8372	*

Notes: T – tumor tissue; N – conditionally normal tissue; C – urine of BC patients; H – urine of healthy individuals; * – sample showing Gaussian distribution; ** – sample showing non-Gaussian distribution.

preserve paired comparison. After outlier removal, the resulting datasets were tested for normality using Shapiro-Wilk test. The number of remaining samples in each group and the results of the normality test are presented in Table 2.

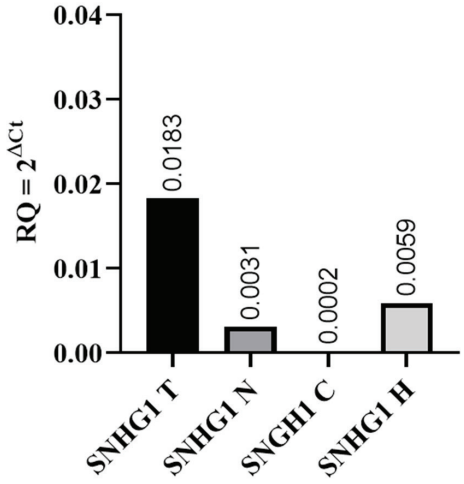

Fig. 1. Relative *SNHG1* gene product quantity in tissues and urine of diseased and healthy individuals.
RQ – relative quantity of *SNHG1* transcripts;
T – tumor tissue; N – conditionally normal tissue;
C – urine of BC patients; H – urine of healthy individuals

The graphical representation of mean *SNHG1* expression levels in the four sample groups (Fig. 1) shows visible differences between the studied groups, calling for statistical comparison. Since tumor tissues and conditionally normal tissues were collected in pairs from the same patients, a parametric paired Student's *t*-test was used to assess differences in central tendency. The calculated t-value (4.363) exceeded the critical value for the 0.01 significance level (3.05). Therefore, a statistically significant difference in *SNHG1* expression levels was observed between tumor and conditionally normal tissue samples.

In the analysis of SNHG1 levels in urine, samples from patients with bladder cancer were compared to those from a control group of healthy individuals. As the data distribution in the patient group showed a non-Gaussian distribution, a non-parametric test (Mann–Whitney *U* test) was used for comparison. The calculated U-value was 0, which is lower than the critical values for significance levels 0.05 (19) and 0.01 (12). This indicates a statistically significant difference in SNHG1 transcript levels in the urine of patients compared to healthy individuals.

Thus, a statistically significant increase in *SNHG1* gene expression was observed in tumor tissues compared to conditionally normal tissues. These findings are consistent with previously reported data showing elevated *SNHG1* expression levels in bladder cancer tissues both *in vitro* and *in vivo* [16,17]. The upregulation of *SNHG1* in tumor tissues compared to adjacent normal tissues in BC patients suggests that SNHG1 may possess a direct role in carcinogenesis. Therefore, further investigation of its expression levels in biological materials appears promising for its potential use as a biomarker of bladder cancer.

In the urine of BC patients, a statistically significant decrease in the relative quantity of SNHG1 was detected compared to urine samples from healthy individuals. For now, no research exists on SNHG1 transcript levels in the urine of bladder cancer patients. Direct comparison of SNHG1 levels in different biological materials is not appropriate as the urine and tissue sample sets only partially overlap. To establish a meaningful correlation between SNHG1 levels in tissues and urine, it is necessary to conduct a parallel study where both types of samples are collected from the same individuals.

To assess the ability of the marker gene to discriminate effectively between BC patients and healthy individuals, an ROC (Receiver Operating Characteristic) curve analysis was performed. This method evaluates the ability of the marker to distinguish between diseased and healthy groups by analyzing the balance between false positive and false negative results. The primary indicator of a marker's diagnostic performance is the AUC (Area Under Curve) value. An AUC value close to 1 indicates a high predictive ability, whereas a value close to 0.5 suggests that the marker performs no better than random guessing [19,20].

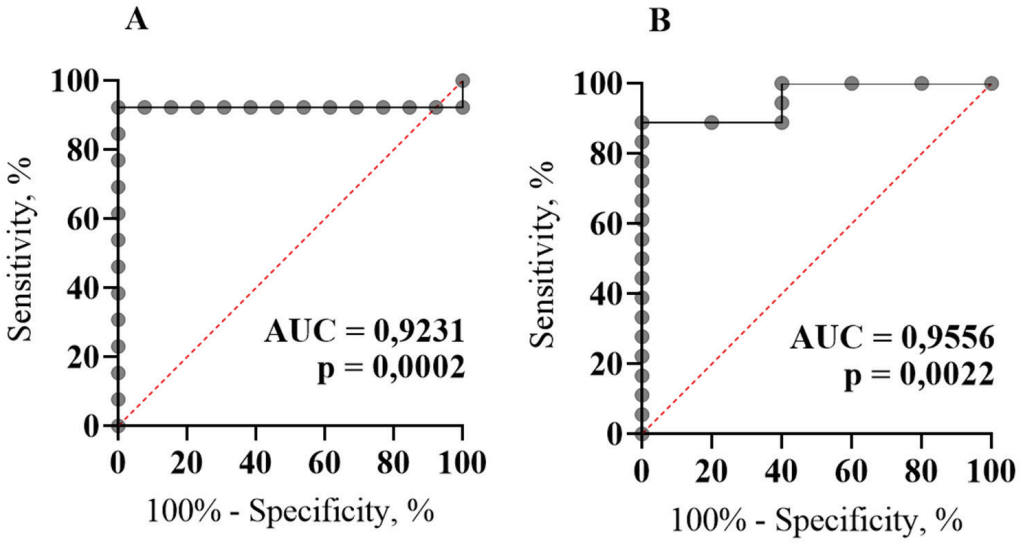

Fig. 2. ROC curves of *SNHG1* transcript quantities in tissue (A) and urine (B) samples

Based on the data on the *SNHG1* relative expression levels in tissue and urine samples, sensitivity and specificity were calculated for various sensitivity threshold levels. Using these calculations, ROC curves were generated for tissue and urine samples. The AUC values and the significance levels of the results are presented in Figure 2.

The resulting graphs illustrate how the sensitivity and specificity of the marker change depending on the given sensitivity threshold. Both remain high for most threshold values, as the AUC value is quite large. This suggests that the marker is highly effective in discriminating between healthy individuals and BC patients. These findings further support the hypothesis that dysregulation of SNHG1 is involved in the oncogenic processes of bladder cancer.

The next step in evaluating the biomarker potential of SNHG1 was to investigate whether its expression levels change with disease progression. At the National Cancer Institute, patient clinical data were obtained, such as age, cancer stage, tumor grade, and previous gemcitabine–cisplatin chemotherapy (Table 3). Analyzing these data may help in determining whether the course of the disease or the applied treatment affects SNHG1 expression, and whether expression levels are associated with patient age. If SNHG1 levels in biological materials change over time with disease progression, this marker could be used not only for diagnosis but also for prognosis and monitoring of the patient's condition.

To assess the potential association between *SNHG1* transcript levels in tissue and urine samples and the clinical parameters of patients, a correlation analysis was performed. Spearman's rank correlation coefficient (r_s) was calculated, as it is suitable for detecting non-linear relations and can be applied to small sample sizes, even when the distribution of values deviates from normality (as in the case with *SNHG1* transcript levels in the urine of cancer patients) (Table 4).

The analysis revealed a correlation between *SNHG1* gene expression levels in tumor tissues and the stage of bladder cancer. This finding is of particular interest, as this relationship possesses the potential to predict disease progression by monitoring changes in the expression level of the marker gene. To determine whether the cancer stage affects *SNHG1* expression levels, a one-way ANOVA (analysis of variance) was performed. However, no statistically significant difference was observed between patient groups (F = 1.285). A possible explanation may be that *SNHG1* expression levels decrease not abruptly but rather gradually over the course of the disease. Thus, we did not find convincing evidence that *SNHG1* expression levels can be used to determine the stage of bladder cancer in patients. Nonetheless, there is some potential for further research to assess whether changes in this parameter with time could be utilized to monitor disease dynamics.

Conclusions

The expression of the gene of the long non-coding RNA SNHG1 is significantly elevated in tumor tissues compared to conditionally normal tissues. This result is expected given the carcinogenic role of SNHG1, which promotes tumor proliferation and growth. In urine samples from patients with bladder cancer, SNHG1 concentration was significantly

decreased compared to the urine of healthy individuals. So far, no studies have been published that analyze *SNHG1* transcript quantity in the urine of bladder cancer patients compared to healthy controls. Therefore, this topic remains open for further investigation.

SNHG1 relative quantities in both types of biological material have shown to be sensitive diagnostic indicators and are effective in distinguishing BC patients from healthy individuals. Additionally, a positive correlation was observed between *SNHG1* gene expression in tumor tissues and cancer stage. Although no statistically significant differences were found between groups of patients at different disease stages, this may indicate that *SNHG1* expression increases gradually and non-linearly during disease progression. Thus, further research is needed to explore the potential of this marker as a prognostic indicator for tumor progression and patient monitoring.

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Table 3

Numbers of patients with various clinical parameters

Groups by clinical parameter	Tissue	Urine
Clinical parameter – age		
35-60	5	10
>60	6	5
No data	2	1
Clinical parameter – cancer stage		
I	1	0
II	4	4
III	4	9
IV	3	3
No data	1	0
Clinical parameter – cancer grade		
G1	1	2
G2	8	7
G3	3	6
Gx/no data	1	1
Clinical parameter – gemcitabine–cisplatin chemotherapy		
Was performed	4	11
Was not performed	6	4
No data	3	1

Table 4

Correlation between SNHG1 transcript levels and patient clinical data

Sample type	Clinical parameter	r_s	Statistical significance
Tissue	Age	-0,1139	$p > 0.05$
	Cancer stage	0,5955	$p < 0.05$
	Tumor grade	-0,0546	$p > 0.05$
	Chemotherapy	0,4975	$p > 0.05$
Urine	Age	0,0991	$p > 0.05$
	Cancer stage	-0,0542	$p > 0.05$
	Tumor grade	0,0059	$p > 0.05$
	Chemotherapy	-0,1759	$p > 0.05$

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ДОВГА НЕКОДУВАЛЬНА РНК SNHG1 ЯК ДІАГНОСТИЧНИЙ ТА ПРОГНОСТИЧНИЙ МАРКЕР РАКУ СЕЧОВОГО МІХУРА

Рак сечового міхура є одним із найпоширеніших онкологічних захворювань у світі. Сучасні методи діагностики раку сечового міхура мають суттєві обмеження. Значний інтерес викликають новітні методи діагностики за допомогою молекулярних маркерів. З-поміж інших епігенетичних механізмів багато довгих некодувальних РНК мають проонкогенні або, навпаки, онкосупресорні властивості. Згідно з дослідженнями, днРНК SNHG1 здатна стимулювати розвиток пухлин та проліферацію злоякісних клітин, водночас пригнічуючи їх апоптоз. **Мета роботи** – оцінити зміни у відносних рівнях експресії днРНК SNHG1 у тканинах пухлин і сечі пацієнтів із раком сечового міхура, а також

визначити її потенціал як діагностичного та прогностичного маркера захворювання. **Методи.** РНК із зразків тканин і сечі екстрагували за допомогою реагенту TRIzol та очищали. На матриці РНК синтезували кДНК та ампліфікували за допомогою ПЛР у реальному часі. Відносні рівні експресії розраховували з первинних даних за формулою $2^{\Delta Ct}$. Зміни рівнів експресії SNHG1 у тканинах пухлин порівняно з умовно здоровими тканинами оцінювали за допомогою t-критерію Стьюдента для попарних порівнянь. Зміни концентрації SNHG1 у сечі хворих порівняно зі здоровими особами досліджували за допомогою критерію Манна – Уітні. Діагностичну здатність обраної днРНК аналізували методом ROC-кривих. Кореляційний аналіз проводили за допомогою рангового коефіцієнта Спірмана, а різницю в рівнях експресії між групами пацієнтів досліджували методом однофакторного дисперсійного аналізу. **Результати.** Виявили статистично значуще підвищення рівня експресії гена SNHG1 у тканинах пухлин порівняно з умовно нормальними тканинами. У сечі пацієнтів із раком сечового міхура спостерігали значне зниження концентрації днРНК SNHG1 порівняно з сечею здорових осіб. ROC-криві для тканин і сечі демонстрували високу діагностичну здатність обраного маркера. Також є позитивна кореляція між рівнем експресії гена SNHG1 у тканинах і стадією раку. Статистично значущих відмінностей у рівнях експресії SNHG1 між групами пацієнтів на різних стадіях захворювання не виявили. **Висновки.** Відносні рівні транскриптів SNHG1 у тканинах і сечі змінюються під час процесів онкогенезу, що свідчить про перспективність подальших досліджень гена SNHG1 як кандидата в маркери раку сечового міхура. Обраний маркер має високу чутливість і специфічність. Зв'язок між рівнем експресії SNHG1 у тканинах і стадією раку також може мати значення для прогнозу захворювання. Для підтвердження отриманих результатів і визначення діагностичної та прогностичної цінності SNHG1 при раку сечового міхура потрібні подальші дослідження.

Ключові слова: рак сечового міхура, епігенетичні біомаркери, днРНК, SNHG1, тканини пухлин, рідинні біопсії.

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