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# ANALYSIS OF *ANRIL* GENE POLYMORPHISM RS4977574 ASSOCIATION WITH KIDNEY CANCER DEVELOPMENT IN UKRAINIAN POPULATION

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**Ключевые слова:** *длинная некодирующая РНК, ANRIL, генетический полиморфизм, рак почки*

**Abstract. Analysis of ANRIL gene polymorphism rs4977574 association with kidney cancer development in Ukrainian population. Volkogon A.D., Harbuzova V.Yu., Ataman A.V.** *ANRIL (Antisense Non-coding RNA in the INK4 Locus, also known as CDKN2B-AS1) – 3.8-kb long non-coding RNA transcribed from the antisense strand of INK4b-ARF-INK4a gene cluster. It is known that ANRIL overexpression is associated with development of oncological pathologies of different localization. In addition, there are a number of studies devoted to role of ANRIL genetic polymorphism in emergence and progression of tumors, including tumors of genitourinary system. The aim of the study was to check the possible association between ANRIL gene polymorphism rs4977574 and kidney cancer development in representatives of Ukrainian population. Whole venous blood of 101 patients with clear cell renal cell carcinoma (CCRCC) (42 women and 59 men) and 100 patients without oncology history (34 women and 66 men) was used in the study. DNA from blood white cells was extracted using GeneJET Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific, USA). Genotyping of rs4977574 ANRIL gene polymorphic locus was performed using real-time polymerase chain reaction (real-time PCR) method in the presence of TaqMan assay C_31720978_30. The mathematical data were processed using the SPSS software package (version 17.0). P values <0.05 were considered as statistically significant. It was found that difference in rs4977574-genotype distribution between patients with CCRCC and control persons was absent in general group (P=0.216). At the same time, the statistical analysis stratified by gender showed that both in female and male subjects rs4977574-genotypes frequency also did not differ significantly between comparison groups (P=0.526 and P=0.160, respectively). However, after adjusting for age, body mass index, and smoking habits statistically significant association between rs4977574 ANRIL gene polymorphism and risk of kidney cancer development was detected in male subjects under superdominant inheritance model (P=0.049). It was revealed that heterozygotes (AG-genotype) have 2.17-fold higher risk of CCRCC development (95% CI=1.005-4.695) compared to patients with AA- and GG-genotypes. In summary, this is the first report about ANRIL gene polymorphisms association with kidney cancer. Obtained results revealed that rs4977574 is related to kidney cancer risk only in Ukrainian men. Male individuals with AG-genotype have higher risk of CCRCC development compared to AA- and GG-genotypes carriers.*

**Реферат. Аналіз зв'язку поліморфізму rs4977574 гена ANRIL із розвитком раку нирки в українській популяції. Волкогон А.Д., Гарбузова В.Ю., Атаман О.В.** *ANRIL (антисмислова некодуюча РНК в локусі INK4, також відома як CDKN2B-AS1) – довга некодуюча РНК довжиною 3,8 кб, що транскрибується з антисмислового ланцюга генного кластеру INK4b-ARF-INK4a. Відомо, що надмірна експресія ANRIL пов'язана із розвитком онкологічних патологій різної локалізації. Крім того, існує ряд досліджень, присвячених ролі генетичного поліморфізму ANRIL у виникненні та прогресії злоякісних пухлин, включаючи пухлини сечостатевої системи. Метою дослідження було встановлення можливого зв'язку між rs4977574-поліморфізмом гена ANRIL та розвитком раку нирок у представників українського населення. У дослідженні було використано цільну венозну кров 101 пацієнта зі світлоклітинним нирково-клітинним раком (СКНКР) (42 жінки та 59 чоловіків) та 100 пацієнтів без онкологічного анамнезу (34 жінки та 66 чоловіків). ДНК з лейкоцитів крові виділяли за допомогою наборів GeneJET Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific, США). Генотипування за поліморфним локусом rs4977574 гена ANRIL проводили за допомогою методу*

*полімеразної ланцюгової реакції в реальному часі (real-time PCR) у присутності TaqMan assay C_31720978_30. Математичні дані обробляли за допомогою програмного пакету SPSS (версія 17.0). Значення P<0,05 вважали за статистично значущі. Було встановлено, що в загальній групі немає різниці в розподілі rs4977574-генотипів між пацієнтами з СКНКР та представниками контролю (P=0,216). При цьому статистичний аналіз, стратифікований за статтю, показав, що як у жінок, так і в чоловіків частота rs4977574-генотипів також суттєво не відрізнялась між групами порівняння (P=0,526 та P=0,160 відповідно). Однак після поправки на вік, індекс маси тіла, наявність звички курити статистично значущий зв'язок між поліморфізмом rs4977574 гена ANRIL та ризиком розвитку раку нирок був виявлений в осіб чоловічої статі в рамках супердомінантної моделі успадкування (P=0,049). Було встановлено, що гетерозиготи (AG-генотип) мають у 2,17 раза більший ризик розвитку СКНКР (95% CI=1,005-4,695) порівняно з пацієнтами з генотипами AA та GG. Таким чином, це перше повідомлення про асоціацію генетичного поліморфізму ANRIL з раком нирок. Отримані результати показали, що rs4977574-локус пов'язаний із ризиком раку нирки лише в українських чоловіків. Особи чоловічої статі з генотипом AG мають більш високий ризик розвитку СКНКР порівняно з носіями AA- та GG-генотипів.*

ANRIL (Antisense Non-coding RNA in the INK4 Locus, also known as CDKN2B-AS1) – 3.8-kb long non-coding RNA (lncRNA) transcribed from antisense strand of INK4b-ARF-INK4a gene cluster [10]. It encodes the amino acid structure of three tumor suppressors: p14ARF, p15INK4b, and p16INK4a. These proteins play a key role in cell cycle arrest, affecting major cellular processes such as senescence, apoptosis, and stem cell self-healing [8].

Today there are a number of reports about relation between ANRIL and development of various oncological pathologies. ANRIL has been found to be overexpressed in gastric cancer [9], esophageal squamous cell carcinoma [12], prostate cancer [15], urinary bladder cancer [11], etc. However, the main molecular mechanism of ANRIL involvement in cancer emergence and progression remains ambiguous.

It is known that in normal cells ANRIL transcript production is required to inhibit the p14ARF, p15INK4b, and p16INK4a expression after DNA repairing. However, abnormal ANRIL expression in cancer cells results in blocking of DNA damage response control, which finally leads to genomic instability and tumor progression [6]. Meseure et al. demonstrated that ANRIL mediates inhibition of INK4a transcription by interacting with CBX7 protein of PRC1 repressor complex (Polycomb repressive complex 1), which in turn leads to silencing [7]. Authors have also revealed significantly increased CBX7 and ANRIL amount and decreased INK4a concentration in breast cancer tissues.

ANRIL also influences cell proliferation by regulating target genes *in trans*. ANRIL has been shown to inhibit the activity of miR-99a/miR-449a in gastric cancer tissues, thereby increasing activity of target genes of these miRNAs – *mTOR* and *CDK6* [9]. On the other hand, in esophageal squamous cell carcinoma ANRIL has been shown to affect cell growth through repression of TGFβ/Smad signaling pathway [12], although the exact molecular mechanisms of interaction between ANRIL and TGFβ1 remain unclear.

Today, there are lot of studies devoted to role of *ANRIL* genetic polymorphism in different tumors occurrence and progression [2, 4, 14, 16], including malignant tumors of genitourinary system [3]. However, studies about association between *ANRIL* gene single-nucleotide variants and risk of kidney cancer development are currently absent.

The aim of the study was to check the possible association between ANRIL gene polymorphism rs4977574 and kidney cancer development in representatives of Ukrainian population.

**MATERIALS AND METHODS OF RESEARCH**

The whole venous blood of 101 patients (42 women and 59 men) with clear cell renal cell carcinoma (CCRCC) and 100 patients (34 women and 66 men) without oncology history was used. Patients were treated at Sumy Regional Clinical Oncology Hospital from 2005 to 2016. The morphological diagnosis of CCRCC was established according to European Association of Urology (EAU) Guidelines [17]. All patients had II stage of cancer according to TNM classification of malignancies.

The study was conducted in compliance with Council of Europe Convention on Human Rights and Biomedicine, the Declaration of Helsinki, and Order of the Ministry of Health of Ukraine № 690 (23.09.2009) [1]. All participants signed the informed consent for venous blood sampling for genetic test. The study protocol was approved by the Ethic Committee of the Medical Institute of Sumy State University (number (№ 3/05.12.11).

DNA from venous blood leukocytes was extracted using GeneJET Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific, USA).

Genotyping of *ANRIL* gene rs4977574 polymorphic locus was performed by real time polymerase chain reaction (Real-Time PCR) using TaqMan Assay C_31720978_30. The reaction was conducted in Quant Studio 5 DX Real-Time instrument (“Applied Biosystems, USA) using PCR Real-Time kit (“Thermo Fisher Scientific”, USA). The amplification reaction consisted of initial 10-minute

denaturation (95 ºC) followed by 45 cycles of amplification for 15 s (95ºC) and 30 s (60°C).

The mathematical data were processed using SPSS software package 17.0.1 version (SPSS Inc. 2147483647). Analysis of rs4977574-genotypes distribution between comparison groups was performed using Pearson's $\chi^2$ test. To check the deviation of rs4977574-genotypes distribution from Hardy-Weinberg equilibrium WpCalc online resource was used (https://wpcalc.com/en/equilibrium-hardy-weinberg/). The risk of CCRCC development, depending on specific rs4977574 genotype, was calculated by logistic regression under dominant (AG+GG vs. AA), recessive (GG vs. AA+AG), and super-dominant (AG vs. AA+GG) models of inheritance. Sex, age, body mass index and smoking status were used as covariates in multivariable regression. HaploReg v4 resource was used for bioinformatics analysis [18]. All tests were two-sided. p values <0.05 were considered as statistically significant.

**RESULTS AND DISCUSSION**

After genotyping of comparison groups by *ANRIL* gene rs4977574-locus we tested the correspondence of AA-, AG- and GG-genotypes frequency to Hardy-Weinberg equilibrium. It was found that both in CCRCC patients and in control subjects rs4977574-genotypes distribution did not deviate from expected by Hardy-Weinberg law (p=0.368 and p=0.252, respectively).

The frequency of rs4977574-genotypes in comparison groups are presented in Table 1. It was found that difference in AA-, AG- and GG-genotypes distribution between CCRCC patients and control group was absent in general group (p=0.216). At the same time statistical analysis stratified by gender showed that rs4977574-genotypes frequency also did not significantly differ between comparison groups both in female (p=0.526) and male (p=0.160).

*Table 1*

***ANRIL* gene rs4977574-genotypes frequency in case and control groups**

| Group | n | Genotype | | | p |
|---|---|---|---|---|---|
| | | AA (%) | AG (%) | GG (%) | |
| **Total** | | | | | |
| CCRCC | 101 | 22 (21.8) | 55 (54.5) | 24 (23.8) | 0.216 |
| Control | 100 | 32 (32.0) | 44 (44.0) | 24 (24.0) | |
| **Female** | | | | | |
| CCRCC | 42 | 10 (23.8) | 22 (52.4) | 10 (23.8) | 0.526 |
| Control | 34 | 11 (32.4) | 18 (52.9) | 5 (14.7) | |
| **Male** | | | | | |
| CCRCC | 59 | 12 (20.3) | 33 (55.9) | 14 (23.7) | 0.160 |
| Control | 66 | 21(31.8) | 26 (39.4) | 19 (28.8) | |

**Note.** CCRCC – clear cell renal cell carcinoma; n – number of persons in the subgroups.

Then to test the possible link between lncRNA *ANRIL* genetic polymorphism and risk of kidney cancer development binary and multivariable logistic regression under different models of inheritance was used (Table 2). Significant association between rs4977574-locus and CCRCC occurrence without adjusting for covariates was not found in general group ($p_c$>0.05) as well as in individuals of different gender ($p_c$>0.05). However, after adjusting for age, body mass index, smoking habits statistically significant relation between *ANRIL* polymorphism rs4977574 and kidney cancer risk was detected in male subjects under superdominant model ($p_{adj}$=0.049). Thus, male heterozygotes (AG-genotype) have higher risk of CCRCC development ($OR_{adj}$=2.172; 95% CI=1.005-4.695) compared to subjects with AA- and GG-genotype.

As of January 2020, 32759 polymorphic sites are located in the *ANRIL* gene (according to NCBI: https://www.ncbi.nlm.nih.gov/snp/?term=CDKN2B-

AS1). Some *ANRIL* gene polymorphisms have significant association with tumor development. Thus, the *ANRIL* TCGA-haplotype (rs1333045, rs1333048 rs4977574 and rs10757278) has been shown to increase breast cancer risk in Iranian women [2]; rs2151280 polymorphism is highly correlated with optic glioma development in neurofibromatosis type 1 patients [14] and linked to relapse in multiple myeloma subjects [16]; wherein locus rs1011970 is related to lung cancer susceptibility and treatment [4]. The authors believe that these nucleotide variations may alter expression of different ANRIL splicing variants and, as a consequence, dysregulate the INK4b-ARF-INK4a locus expression.

*Table 2*

**Analysis of *ANRIL* rs4977574 genotypic association with CCRCC risk**

| Model | $p_c$ | $OR_c$ (95% CI) | $p_{adj}$ | $OR_{adj}$ (95% CI) |
|---|---|---|---|---|
| **Total** | | | | |
| **Dominant** | **0.104** | **1.690 (0.898-3.108)** | **0.193** | **1.555 (0.800-3.024)** |
| **Recessive** | **0.968** | **0.987 (0.516-1.888)** | **0.592** | **0.827 (0.413-1.656)** |
| **Superdominant** | **0.139** | **1.522 (0.873-2.654)** | **0.111** | **1.610 (0.896-2.894)** |
| **Female** | | | | |
| **Dominant** | **0.409** | **1.530 (0.557-4.203)** | **0.426** | **1.514 (0.545-4.210)** |
| **Recessive** | **0.325** | **1.812 (0.554-5.930)** | **0.391** | **1.697 (0.507-5.687)** |
| **Superdominant** | **0.961** | **0.978 (0.395-2.419)** | **0.968** | **1.019 (0.405-2.562)** |
| **Male** | | | | |
| **Dominant** | **0.149** | **1.828 (0.806-4.144)** | **0.320** | **1.562 (0.648-3.765)** |
| **Recessive** | **0.522** | **0.770 (0.345-1.717)** | **0.200** | **0.563 (0.234-1.355)** |
| **Superdominant** | **0.066** | **1.953 (0.957-3.982)** | **0.049** | **2.172 (1.005-4.695)** |

**Note.** CCRCC – clear cell renal cell carcinoma; 95% CI – 95% confidence interval; $P_c$ – crude P (without adjusting for covariates); $OR_c$ – crude odds ratio; $P_{adj}$ – P after adjusting for sex (in total group), age, body mass index and smoking status; $OR_{adj}$ – adjusted odds ratio.

Taheri M. et al. tested the link between prostate cancer, benign prostate hyperplasia and four *ANRIL* gene polymorphisms (rs1333045, rs4977574, rs1333048, and rs10757278) in Iranian patients [3]. It was shown that rs4977574, rs1333048, and rs10757278 are associated with prostate tumors occurrence origin.

Polymorphism rs4977574 is located within 16 intron of *ANRIL* gene (103785th gene position). Functional studies devoted to its role in diseases development are currently absent, but bioinformatic analysis using HaploReg v4 resource [18] revealed that rs4977574 polymorphism can change nucleotide sequence of transcription factor C-ets-1 and glucocorticoid receptor binding sites. Studies have shown significant role of these proteins in the origin and progression of kidney cancer [5, 13]. Thus, it can be assumed that *ANRIL* polymorphism rs4977574 is able to promote cancer development through the modulation of impact of mentioned transcription factors on lncRNA ANRIL expression.

In our study we firstly established the *ANRIL* rs4977574-genotypes distribution among Ukrainian population and examined the association of this polymorphism with kidney cancer development. The link between rs4977574 single-nucleotide polymorphism and CCRCC has been found only in men. After adjusting for covariates it was revealed that men with genotype rs4977574AG have higher risk of CCRCC development compared to men with rs4977574AA- and rs4977574GG-genotypes.

**CONCLUSION**

In summary, this is the first report about *ANRIL* gene polymorphisms association with kidney cancer. Obtained results revealed that locus rs4977574 is related to kidney cancer risk only in Ukrainian men.

Male individuals with AG-genotype have higher risk of CCRCC development compared to AA- and GG-genotypes carriers.

Conflict of interests. The authors declare no conflict of interest.

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