ORIGINAL ARTICLE

CONTENTS

Analysis of the association of rs1333049-polymorphic variants of the *ANRIL* gene with the development of clear cell renal cell carcinoma in Ukrainian population

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ABSTRACT

Aim: The study aimed to assess the association between rs1333049 polymorphic variants of the *ANRIL* gene and the development of clear cell renal cell carcinoma in the Ukrainian population.

Materials and Methods: Venous blood from 201 individuals was analyzed, including 101 ccRCC patients (42 women, 59 men) and 100 cancer-free controls (34 women, 66 men). *ANRIL* rs1333049 genotyping was performed using real-time PCR, with statistical analysis conducted via Prism (v10.4.1) and R (v4.4.2).

Results: The rs1333049 genotype distribution in ccRCC patients was GG – 16 (15.8%), GC – 50 (49.5%), CC – 35 (34.7%); in controls: 28 (28%), 49 (49%), 23 (23%) (P=0.0561). The C allele was more frequent in ccRCC patients (P=0.0167). In the dominant model, GC+CC carriers had a 2.066-fold higher risk than GG homozygotes (P=0.0392). No genotype differences were found between sexes in controls (P=0.39), but allele distribution differed in male and female ccRCC patients (P=0.0105). In the recessive model, males with CC had a 2.5-fold higher ccRCC risk (P=0.02). Kaplan-Meier analysis found no effect of rs1333049 on overall survival.

Conclusions: The rs1333049 polymorphism of the *ANRIL* gene increases ccRCC risk. GC and CC genotypes raise risk 2.07-fold (P=0.0392), up to 3.1-fold (P=0.040) after adjustments. In males, CC genotype increases risk 2.5-fold (P=0.02) and 3.12-fold (P=0.05) after adjustments. No link to overall survival was found (P=0.4321).

KEY WORDS: gene polymorphism, long non-coding RNA, *ANRIL*, clear cell renal cell carcinoma (ccRCC)

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INTRODUCTION

According to the International Agency for Research on Cancer (IARC), approximately one in five men or women will develop cancer in their lifetime, and approximately one in nine men and one in 12 women will die from it. Given demographic projections, the number of new cancer cases is expected to reach 35 million by 2050 [1].

Regarding statistical data for Ukraine, in the overall structure of malignant diseases among men, kidney cancer ranks 7th (5.6%) and among women – 9th (2.9%) [2]. Clear cell renal cell carcinoma (ccRCC) accounts for approximately 95% of all cases of malignant kidney tumors [3]. Therefore, the development of methods for accurate diagnosis, individual treatment, and early prevention of ccRCC is an important direction of modern fundamental and applied medical science.

Today, several genetic factors are known that are predictors of the development of ccRCC [4, 5], including single nucleotide polymorphisms (SNPs) of genes involved in the processes of cell division and differentiation. As shown by numerous experimental studies, long noncoding RNAs (lncRNAs) play a crucial role in the occurrence and progression of tumors of various localization, providing molecular regulation of cell division and transformation [6,7]. Given this, lncRNAs are not only promising markers for early diagnosis of cancer diseases, but also important factors in targeted therapy [8-10].

Special attention in the study of the pathogenesis of malignant tumors is currently given to lncRNA *ANRIL* (Antisense Non-coding RNA in the INK4 Locus). *ANRIL* is transcribed from the antisense strand of the INK4b-ARF-INK4a gene cluster (chromosome 9, region p21.3). This gene cluster encodes three important tumor suppressors – p14ARF, p15INK4b, and p16INK4a – which play a crucial role in cell cycle arrest.

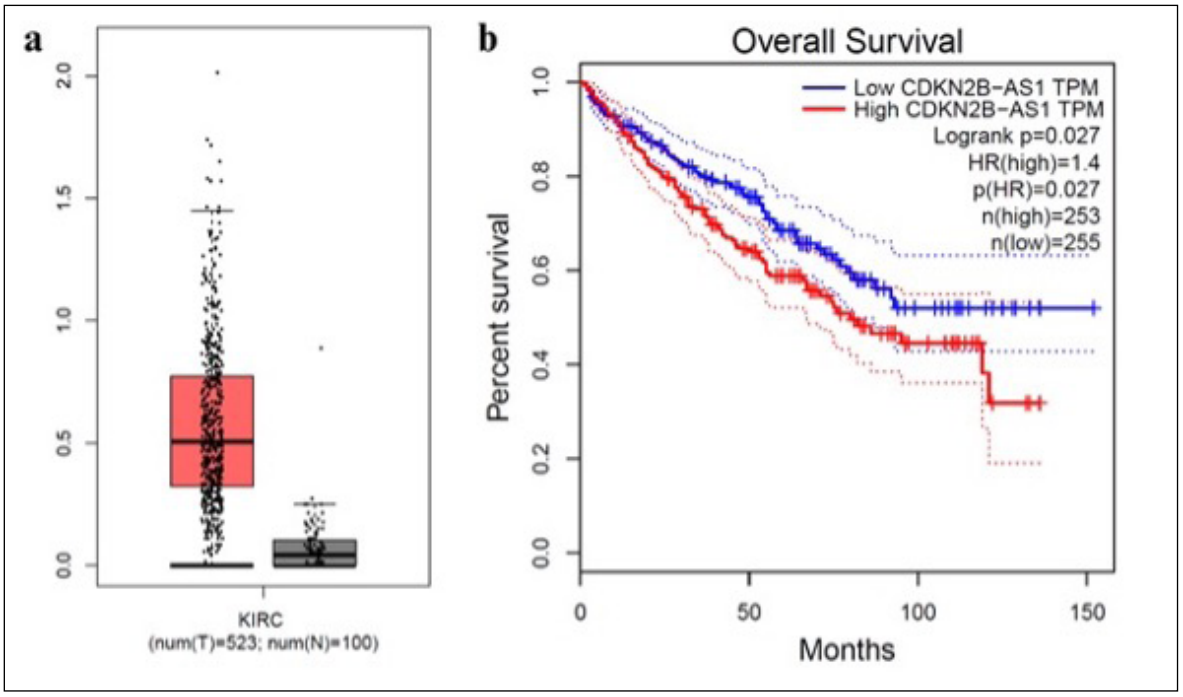

Fig. 1. *ANRIL* expression levels in kidney tumors compared to the control group based on GEPIA data
Picture taken by the authors

Although the primary molecular mechanism by which ANRIL increases the risk of cancer progression remains unclear, it is believed that this risk is associated with high levels of gene expression. Studies have shown that excessive expression of *ANRIL* suppresses the activity of p14ARF, p15INK4b, and p16INK4a, leading to genomic instability and promoting tumor progression [11].

Recent experimental research has confirmed *ANRIL's* involvement in the development of various malignant tumors [9], including gastric cancer [12], bladder cancer [13, 15], prostate cancer [14], esophageal cancer [16], hepatocellular carcinoma [17], breast cancer [18], and lung cancer [19].

Using GEPIA (http://gepia.cancer-pku.cn/), an application that analyzes available gene expression data, we found that ANRIL levels are significantly higher in kidney tumors compared to controls (Fig. 1a). Furthermore, elevated ANRIL expression is associated with poorer patient survival (Fig. 1b), confirming a potential link between ANRIL and kidney tumor progression.

Regarding the role of *ANRIL* gene polymorphic variants in kidney cancer development, research remains limited. Notably, studies indicate that males carrying the *AG* genotype of the rs4977574 polymorphism have a higher risk of developing clear cell renal carcinoma (ccRCC) compared to individuals with *AA* or *GG* genotypes [20]. However, no data currently exist on the association of the rs1333049 polymorphism with oncological diseases of the urinary system.

AIM

The aim of our study was to study the possible association between the rs1333049 polymorphism of the *ANRIL* gene and the development of clear cell renal cell carcinoma in the Ukrainian population.

MATERIALS AND METHODS

The study included 201 participants, consisting of 101 patients with clear cell renal carcinoma (ccRCC) (42 women and 59 men) and 100 individuals without an oncological history (34 women and 66 men). The clinical characteristics of the patients and control group are presented in Table 1.

The final morphological diagnosis of ccRCC was verified in accordance with the European Association of Urology Guidelines (EAU) [21]. All patients were diagnosed with Stage II cancer, according to the TNM classification of malignant tumors, based on histological examination or MRI results. Individuals with tumors of other locations, hereditary diseases, or conditions of unknown etiology were excluded from the study group.

The study protocol was approved by the Bioethics Committee of the Educational and Scientific Medical Institute of Sumy State University (No. 5/07.2022) and complies with Order No.690 of the Ministry of Health of Ukraine (dated September 23, 2009) [22] as well as the Declaration of Helsinki on ethical principles for medical research involving human subjects. All participants provided written informed consent for personal data processing, blood sampling, and genetic analysis.

Table 1. General clinical characteristics of patients with ccRCC and control group individuals

Characteristics	ccRCC	Control group	P
Age, years	61.62	77.38	<0.000001
Body weight, kg	78.49	74.31	0.021181
Height, cm	170.7	165.8	0.000561
Body mass index	27.01	27,13	0.851827
Blood glucose, mmol/l	54.99	52.68	0.238665
Gender, f/m	42/59	34/66	0.3093
Smokers (%)	49 (48.5)	27 (27.0)	0.0022
Obesity (%)	30 (29.7)	18 (18.0)	0.0683

Note: ccRCC – clear cell renal cell carcinoma, n – number of patients; f – women; m – men; P – statistical significance of differences. Categorical variables were compared using the χ2-test, quantitative vari
Source: compiled by the authors of this study

Table 2. Frequencies of alleles and genotypes according to the rs1333049 polymorphism of the *ANRIL* gene in patients with ccRCC and individuals of the control group

	ccRCC		Control group		P (χ^2)
	n	%	n	%	
Genotypes					
GG	16	15.8	28	28	0.0561 (5.761)
GC	50	49.5	49	49	
CC	35	34.7	23	23	
Alleles					
G	82	40.6	105	52.5	0.0167 (5.726)
C	120	59.4	95	47.5	

Note: ccRCC – clear cell renal cell carcinoma, n – number of patients; P – Pearson's χ2 test for significance of differences
Source: compiled by the authors of this study

To investigate the rs1333049 polymorphism of the ANRIL gene, venous blood was collected under sterile conditions into 2.7 ml Monovette tubes containing potassium salt of ethylenediaminetetraacetic acid (EDTA, 11.7 mM) as an anticoagulant ("Sarstedt," Germany). Blood samples were frozen and stored at -20°C. DNA extraction from whole blood leukocytes was performed using the GeneJET Whole Blood Genomic DNA Purification Mini Kit ("Thermo Fisher Scientific," USA). Genotyping of the rs1333049 polymorphic locus of the ANRIL gene was carried out at the Scientific Laboratory of Molecular-Genetic Research of Sumy State University using the real-time polymerase chain reaction (Real-time PCR) method on a Quant Studio 5 DX Real-Time system ("Applied Biosystems," USA). The study utilized TaqMan assays (TaqMan® SNP Assay C___1754666_10) and a PCR Real-Time reagent kit («Thermo Fisher Scientific," USA). Amplification conditions included an initial denaturation at 95°C for 10 minutes, followed by 45 cycles consisting of 15 seconds at 95°C and 30 seconds at 60°C. The generated amplification curves were analyzed using the software provided with Quant Studio 5 DX Real-Time.

Statistical analysis of the obtained data was performed using Prism software (version 10.4.1) and R software (version 4.4.2). The distribution of rs1333049 genotypes between groups was assessed using Pearson's chi-square (χ^2) test. Hardy-Weinberg equilibrium (HWE) was tested using the Equilibrium WpCalc online resource (https://wpcalc.com/en/equilibrium-hardy-weinberg/). The risk of developing ccRCC depending on the rs1333049 genotype was calculated using logistic regression, considering different inheritance models: Dominant model (GG vs. GC+CC), Recessive model (GG+GC vs. CC), Overdominant model (GG+CC vs. GC). To assess the association of rs1333049 polymorphic variants with ccRCC risk, adjusting for gender, age, body mass index (BMI), and smoking status, a multivariable logistic regression model was applied. Overall survival analysis was conducted using the Kaplan-Meier method. All statistical tests were two-tailed, and p-values <0.05 were considered statistically significant.

RESULTS

As a result of the study, the distribution of genotypes and alleles for the rs1333049 polymorphism of the

Table 3. Analysis of the association of the rs1333049 polymorphism of the *ANRIL* gene with ccRCC considering different inheritance models

Model	P_{obs}	OR_{obs} (95 % CI)	P_{adj}	OR_{adj} (95 % CI)
Dominant	0.0392	2.066 (1.04 - 4.11)	0.040	3.1 (1.05 - 9.18)
Recessive	0.0698	1.770 (0.95 – 3.301)	0.065	2.36 (0.94 – 5.89)
Over dominant	0.9430	1.020 (0.587 – 1.77)	0.990	0.996 (0.437 – 2.27)

Note: ccRCC – clear cell renal cell carcinoma, 95% CI – 95% confidence interval; P_{obs} – observed P value (without adjustment for covariates); ORobs – observed odds ratio; Padj – P value after adjustment for age, sex, smoking habit and BMI; ORadj– odds ratio after adjustment for covariates
Source: compiled by the authors of this study

Table 4. Frequency of alleles and genotypes according to the rs1333049 polymorphism of the *ANRIL* gene in patients with ccRCC and control group individuals of different genders

Group	Genotypes						P_1
	GG		GC		CC		
	n	%	n	%	n	%	
Male							
ccRCC	25	42.4	24	40.7	10	16.9	0.275 (2.577)
Control	19	28.8	32	48.5	15	22.7	
Female							
ccRCC	6	14.3	26	61.9	10	23.8	0.39 (1.885)
Control	9	26.5	17	50.0	8	23.5	
P_2 = 0.0105 (9.122); P_3 = 0.97 (0.0598)							

Note: ccRCC – clear cell renal cell carcinoma, n – number of patients; P_1 – significance level of differences between patients with SCRC and controls, P_2 – significance level of differences between patients of different sexes; P_3 – significance level of differences between individuals of the control group of different sexes (Pearson's χ2-test).
Source: compiled by the authors of this study

ANRIL gene was examined in patients with clear cell renal cell carcinoma (ccRCC) and individuals from the control group (Table 2). It was shown that the minor C allele was more frequently detected in ccRCC patients compared to the control group (P = 0.0167; $\chi^2 = 5.726$). The genotype distribution for this polymorphism in the ccRCC group was as follows: GG – 16 (15.8%), GC – 50 (49.5%), CC – 35 (34.7%). In the control group, the distribution was GG – 28 (28%), GC – 49 (49%), CC – 23 (23%). The P-value, calculated using Pearson's χ^2 test, was close to statistical significance (P = 0.0561).

The association between the rs1333049 polymorphism of the *ANRIL* gene and ccRCC was analyzed using binary and multivariable logistic regression under different inheritance models (Table 3). According to the dominant model, carriers of the minor allele (GC+CC) had a 2.066-fold increased risk of developing the disease compared to homozygotes for the major allele (GG) (P = 0.0392). After adjusting for age, sex, smoking status, and BMI, the association remained statistically significant, with the risk increasing to 3.1 times (P = 0.040).

The next step in the analysis was to examine the sex-specific differences in the association of the rs1333049 polymorphism of the ANRIL gene with ccRCC. Table 4 presents the genotype frequency distribution for the rs1333049 locus in male and female ccRCC patients and control individuals. Among male patients, the genotype distribution was GG – 25 (42.4%), GC – 24 (40.7%), CC – 10 (16.9%), while in the male control group, it was GG – 19 (28.8%), GC – 32 (48.5%), CC – 15 (22.7%) (P = 0.275). Among female patients, the genotype distribution was GG – 6 (14.3%), GC – 26 (61.9%), CC – 10 (23.8%), whereas in the female control group, it was GG – 9 (26.5%), GC – 17 (50.0%), CC – 8 (23.5%). No significant differences in genotype distribution were found between control group individuals of different sexes (P = 0.39). However, the allelic distribution of rs1333049 differed significantly between male and female ccRCC patients (P = 0.0105).

Table 5 shows the results of the regression analysis of the association of the rs1333049 polymorphism of the *ANRIL* gene with the development of ccRCC separately in the groups of women and men with ccRCC. In the group of women, no genotype-dependent increase in the risk of developing ccRCC was detected in any inheritance model.

However, according to the recessive inheritance model, the risk of developing ccRCC in males with the CC genotype is 2.5 times higher than in carriers of the GG

Table 5. Analysis of the association of the rs1333049 polymorphism of the *ANRIL* gene with the development of ccRCC in individuals of different sexes, considering different inheritance models

Model	P_{obs}	OR_{obs}	P_{adj}	OR_{adj}
		Male		
Dominant	0.12	0.5 (0.21 – 1.19)	0.49	0.64 (0.18 – 2.25)
Recessive	0.02	2.5 (1.15 – 5.42)	0.05	3.12 (1.0 – 9.75)
Over dominant	0.38	0.73 (0.36 – 1.48)	0.20	0.5 (0.17 – 1.43)
		Famale		
Dominant	0.19	0.46 (0.15 – 1.46)	0.055	0.145(0.02 – 1.04)
Recessive	0.98	1.01 (0.35 – 2.94)	0.33	2.46 (0.4 – 15.6)
Over dominant	0.3	1.62 (0.65 – 4.06)	0.14	3.6 (0.65 – 19.7)

Note: ccRCC – clear cell renal cell carcinoma; 95% CI – 95% confidence interval; P_{obs} – observed P value (without adjustment for covariates); OR_{obs} – observed odds ratio; P_{adj} – P value after adjustment for age, sex, smoking habit and BMI; OR_{adj} – odds ratio after adjustment for covariates
Source: compiled by the authors of this study

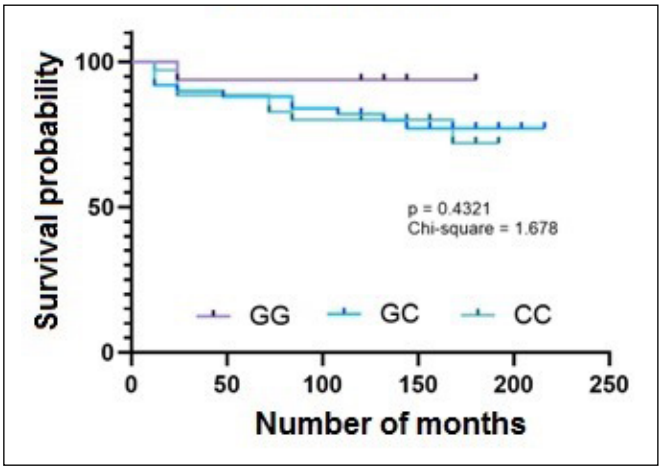

Fig. 2. Overall Survival of Patients with ccRCC Depending on Genotype
Picture taken by the authors

and GC genotypes (P = 0.02). After adjusting for age, sex, smoking habit and BMI, the risk increased to 3.12 times (P = 0.05).

To assess the impact of the rs1333049 polymorphism of the *ANRIL* gene on the overall survival of patients with ccRCC, a survival analysis was performed using the Kaplan-Meier method (Fig.2).

In the group of GG-genotype carriers, 1 fatal case was recorded, among GC carriers – 11, and among CC carriers – 8. Statistical analysis did not reveal a significant relationship between the genotype according to the rs1333049 polymorphism of the *ANRIL* gene and overall survival (P=0.4321).

DISCUSSIONS

The first studies on the role of long non-coding RNAs in the development of pathological processes and diseases were devoted to the pathology of the cardiovascular system, including in the Ukrainian population [23-25]. Later, given the great importance of long noncoding RNAs in the regulation of cell division and transformation [26], the efforts of scientists were directed to studying the role of these molecules as possible markers of the development of malignant tumors and their malignancy [27-29].

In normal cells, elevated levels of *ANRIL* transcripts play an important role in suppressing the formation of tumor suppressors p14ARF, p15INK4b, and p16INK4a and DNA repair. However, in cancer cells, overexpression of *ANRIL* has negative consequences – it causes genome instability and promotes tumor development [30]. D. Meseure et al. explained the mechanism of action of the long non-coding RNA ANRIL [31]. The authors proved that the interaction of *ANRIL* with *CBX7*, which is a component of the PRC1 (Polycomb repressive complex 1) repressor complex, inhibits the transcription of p16INK4a. In the laboratory of Zhao J., it was found that ANRIL affects the proliferation of cancer cells through inhibition of the TGFβ/Smad signaling cascade [31]. However, the exact molecular mechanisms by which ANRIL interacts with TGFβ1 still remain unclear.

The long non-coding RNA *ANRIL* (also known by its official name *CDKN2BAS1*) is encoded by a gene consisting of 21 exons and 20 introns. This gene is located on the short arm of chromosome 9, in the 9p21.3 region, within the INK4b-ARF-INK4a gene cluster. According to the National Center for Biotechnology Information (NCBI), as of early 2025, 52,654 polymorphic sites have been identified in the ANRIL gene (https://www.ncbi.nlm.nih.gov/snp/?term=CDKN2B-AS1+homo+sapience). Based on the GRCh38/hg38 genome assembly, the single nucleotide polymorphism (SNP) rs1333049 (G/C) of ANRIL is located at position 22,125,504 within the 3'-untranslated region (3'-UTR) of the gene.

The number of studies investigating the role of the rs1333049 polymorphism in the long non-coding RNA *ANRIL* gene in tumor development is limited. Research

by S. Seifi et al. has shown that carriers of the minor CC and CG alleles have an increased risk of developing breast cancer compared to individuals with the GG genotype [33]. Additionally, the rs1333049 polymorphism has been proven to play a role in the development of gastric cancer [34]. Studies have also revealed that this polymorphism is associated with an increased risk of breast cancer and mortality in patients with diabetes [35]. Furthermore, it has been demonstrated that the CC genotype is linked to reduced overall survival in patients with esophageal squamous cell carcinoma [36]. Moreover, research by Y. Chen et al. found that lung cancer patients with the CC genotype at rs1333049 in the *ANRIL* gene undergoing platinum-based chemotherapy had a lower risk of cancer progression and significantly longer progression-free survival compared to patients with the GG and GC genotypes [35].

Our study demonstrated an association between the rs1333049 polymorphism and the development of clear cell renal cell carcinoma (ccRCC) in the Ukrainian population. Specifically, individuals carrying the minor allele exhibited a higher risk of developing the disease compared to those who were homozygous for the major allele (P = 0.0392). However, no significant effect on overall survival in ccRCC patients was observed.

Currently, there is no additional data on the association between the rs1333049 polymorphic locus of the *ANRIL* gene and tumor development in the urinary system in both the Ukrainian and other populations. Given the critical role of *ANRIL* in cell differentiation and division, studying its single nucleotide polymorphisms (SNPs) remains a highly relevant direction in identifying genetic markers for cancer diagnostics and personalized treatment.

CONCLUSIONS

An association of the rs1333049 polymorphism of the *ANRIL* gene with the development of clear cell renal cell carcinoma was found in the Ukrainian population: carriers of the minor allele (GC+CC) had a higher risk of developing the disease than homozygotes for the major allele (GG) (according to binary logistic regression, 2.066 times (P=0.0392); according to multivariable logistic regression, after adjusting for age, sex, smoking habit and BMI, – 3.1 times (P=0.040).

It has been proven that in males with the CC genotype, the risk of developing ccRCC is 2.5 times higher than in carriers of the GG and GC genotypes (P=0.02). Considering the adjustment for age, sex, smoking habit and BMI, the risk increases to 3.12 times (P=0.05).

No significant association between the genotype of the rs1333049 polymorphism of the *ANRIL* gene and overall survival of patients with ccRCC (P=0.4321).

PROSPECTS FOR FURTHER RESEARCH

To investigate the association of polymorphisms of other long non-coding RNAs in the development of clear cell renal cell carcinoma in order to predict the risk of developing the disease.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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