MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

2, Rymskogo-Korsakova st., Sumy 40007, Ukraine
e-mail: EUMJ@med.sumdu.edu.ua
eumj.med.sumdu.edu.ua
ISSN: 2663-5909 (print)

DOI: https://doi.org/10.21272/eumj.2022;10(2):147-154

ABSTRACT

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ANALYSIS OF THE ASSOCIATION OF RS4977574-POLYMORPHIC VARIANTS OF THE ANRIL GENE WITH THE DEVELOPMENT OF ACUTE CORONARY SYNDROME IN INDIVIDUALS WITH DIFFERENT BODY MASS INDEX IN THE UKRAINIAN POPULATION

The **objective** was to analyze the association of rs4977574-polymorphic variants of the ANRIL gene with the development of acute coronary syndrome in individuals with different body mass index.

Materials and methods. The venous blood of 429 people (234 patients with acute coronary syndrome and 195 people in the control group) was used for the study. Genotyping of patients by rs4977574-polymorphic variants of the ANRIL gene was performed by real-time polymerase chain reaction (Real-time PCR) in the presence of TaqMan assay C_31720978_30. Statistical analysis of the results of the study was performed using SPSS software (version 17.0).

Results. The distribution of genotypes according to SNP rs4977574 of the ANRIL gene in the group of patients with ACS and the control group among individuals with BMI < 25 kg/m^2 does not differ. Among patients with BMI 25 kg/m^2 the genotype distribution of the rs4977574-polymorphic variant of the ANRIL gene was statistically significant ($p = 0.035$). In the group of patients with BMI > 25 kg/m^2 according to recessive ($P_{observ} = 0.014$; $OR_{observ} = 1.876$, 95 % CI = 1.137–3.095) and additive ($P_{observ} = 0.014$; $OR_{observ} = 2.118$, 95% CI = 1.166–3.849) models of inheritance before making adjustment, people with G/G genotype had a double risk of acquiring ACS than carriers of the dominant allele. After the adjustment, corresponding models of inheritance had the same risk rate – for recessive model ($P_{adjust} = 0.013$; $OR_{adjust} = 1.951$, 95% CI = 1.149–3.313) and additive model ($P_{adjust} = 0.026$; $OR_{adjust} = 2.039$, 95 % CI = 1.087–3.826).

Conclusions. Individuals with BMI > 25 kg/m^2, which were carriers of G/G genotype had a 2 times higher risk to acquire ACS than the individuals with the dominant allele.

Prospects for further research. Further research will be aimed at studying the impact of ANRIL polymorphism upon the risk of ACS development depending on other risk factors.

Keywords: gene polymorphism, ANRIL, rs4977574, acute coronary syndrome.

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РЕЗЮМЕ

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АНАЛІЗ ЗВ'ЯЗКУ RS4977574-ПОЛІМОРФНИХ ВАРІАНТІВ ГЕНА ANRIL ІЗ РОЗВИТКОМ ГОСТРОГО КОРОНАРНОГО СИНДРОМУ В ОСІБ З РІЗНИМ ІНДЕКСОМ МАСИ ТІЛА В УКРАЇНСЬКІЙ ПОПУЛЯЦІЇ

Мета роботи – проаналізувати зв'язок rs4977574-поліморфних варіантів гена ANRIL із виникненням гострого коронарного синдрому в осіб з різним індексом маси тіла.

Матеріал і методи. Для дослідження було використано венозну кров 429 осіб (234 хворих з гострим коронарним синдромом та 195 осіб групи контролю). Для генотипування пацієнтів за поліморфізмом rs4977574 гена ANRIL проводили за допомогою полімеразної ланцюгової реакції в режимі реального часу (Real-time PCR) за наявності TaqMan assay C_31720978_30. Статистичне опрацювання результатів дослідження було проведено з використанням програмного забезпечення SPSS (версія 17.0).

Результати. Розподіл генотипів за SNP rs4977574 гена ANRIL у групі хворих на ГКС та групі контролю серед осіб з ІМТ < 25 кг/м^2 не відрізняється. Серед пацієнтів з ІМТ > 25 кг/м^2 розподіл генотипів за rs4977574 поліморфним варіантом гена ANRIL є статистично значущим (p = 0,035). У групі пацієнтів з ІМТ > 25 кг/м^2 згідно рецисивної ($P_{спост}$ = 0,014; $OR_{спост}$ = 1,876, 95 % CI = 1,137–3,095) та адитивної ($P_{спост}$ = 0,014; $OR_{спост}$ = 2,118, 95 % CI = 1,166–3,849) моделей успадкування, до внесення поправок, особи з G/G-генотипом мають ризик захворіти на ГКС у 2 рази більший, ніж носії домінантного алелю. Після поправок, у відповідних моделях успадкування ризик зберігається – рецисивна ($P_{попр}$ = 0,013; $OR_{попр}$ = 1,951, 95 % CI = 1,149–3,313) та адитивна ($P_{попр}$ = 0,026; $OR_{попр}$ = 2,039, 95 % CI = 1,087–3,826).

Висновки. Особи з ІМТ > 25 кг/м^2, які є носіями G/G-генотипу мають ризик захворіти на ГКС у 2 рази більший, ніж особи з домінантним алелем.

Перспективи подальших досліджень. Подальші дослідження будуть спрямовані на встановлення впливу поліморфізму ANRIL на ризик розвитку ГКС в залежності від інших факторів ризику.

Ключові слова: поліморфізм генів, ANRIL, rs4977574, гострий коронарний синдром.

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How to cite/ Як цитувати статтю: Kniazkova PV, Harbuzova VYu. Analysis of the association of rs4977574-polymorphic variants of the ANRIL gene with the development of acute coronary syndrome in individuals with different body mass index in the Ukrainian population. *EUMJ*. 2022;10(2):147-154
DOI: https://doi.org/10.21272/eumj.2022;10(2):147-154

INTRODUCTION/ВСТУП

It is known that there are about 20 thousand protein-encoding genes that make up less than 2% of the total human genome [1, 2]. For a long time, the other 98% were thought to be transcriptional "noise" or "evolutionary garbage" caused by the inclusion of mobile genetic elements. Because of this, one of the biggest surprises in modern science has been the discovery that non-coding RNAs (ncRNAs), which have little or no protein-coding ability, can play an important role in the development of organisms, their physiology and

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pathology [3, 4, 5]. ncRNAs are divided according to various classifications, for example by length, which is measured by the number of nucleotides. Scientists around the world take great interest in long non-coding RNA (lncRNA) consisting of 200 and more nucleotides.

lncRNA occupy a large proportion of the protein-noncoding genome and may be involved in various critical biological processes, such as protein transport, transcription, translation, participation in cell differentiation, etc., which implies their impact on a wide range of multifactorial human diseases [6–10].

Scientists are especially attracted by ANRIL (Antisense Non-coding RNA in the INK4 Locus) or CDKN2B-AS1 (Cyclin-dependent kinase inhibitor 2B antisense RNA 1) – lncRNA, which consists of 3834 nucleotides and is transcribed from the antisense chain of the gene cluster INK4b-ARF-INK4a [11, 12]. rs4977574-polymorphism of this gene is one of the most studied and, according to different researches, is connected to lots of multifactorial diseases [15, 16]. For example, a recent study by Huang et al. found an association of SNP rs4977574 with overall risk of carcinogenesis [13], and Qiao et al. found an effect on glucose metabolism and the development of type 2 diabetes [14].

Probably, since the occurrence of acute coronary syndrome (ACS) depends on both genetic factors and environmental factors, and also occupies one of the first places in prevalence, this disease is a multifactorial disease, the study of which is particularly promising today. A meta-analysis of several studies has shown that SNP rs4977574 CDKN2BAS gene has a strong association with ACS in American–Caucasian and European groups [17]. Several broad genomic studies (Genome-wide association study (GWAS)) found that rs4977574-polymorphism is also associated with the development of ACS and myocardial infarction in different ethnic groups [18, 19].

Given the extremely large number of ACS patients diagnosed each year and the prevalence of both bad habits and sedentary and irresponsible lifestyles, studying the relationship between genetic factors and other risk factors is incredibly important.

The aim of the study. Analyze the distribution rs4977574-polymorphic variants of the ANRIL gene in individuals with acute coronary syndrome with different body mass index.

Materials and methods

The study involved 429 patients, of whom 195 were patients with ACS and 234 – the control group.

All patients with ACS were treated in the cardiology departments of Sumy regional clinical hospital for war veterans and Sumy regional clinical hospital. The diagnosis of acute myocardial infarction and unstable angina was established on the basis of clinical, biochemical and ECG examination in accordance with the recommendations of the European Society of Cardiology [20].

Patients with cardiogenic shock, severe renal and hepatic insufficiency, bronchial asthma, trauma or major surgery, acute or chronic inflammation in the acute phase, malignant tumors and systemic diseases were excluded from the study.

The control group included relatively healthy individuals. The absence of cardiovascular pathology was confirmed by collection of anamnestic data, ECG recording, blood pressure measurement and study of blood biochemical parameters.

The study corresponds to the main provisions of the Council of Europe Convention on Human Rights and Biomedicine, the Declaration of Helsinki and the Order of the Ministry of Health of Ukraine № 690 from 23.09.2009. The study protocol was approved by the Commission on Bioethics of the Medical institute of Sumy state university (No. 1/11 of 12.11.2018). All participants provided written informed consent to participate in the molecular genetic study prior to the collection of the material.

Blood leukocyte DNA was isolated using a commercial kit GeneJET Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific, CIIIA). Genotyping of patients by polymorphism rs4977574 of the ANRIL gene was performed by polymerase chain reaction in real time (Real-time PCR) in the presence TaqMan assay C_31720978_30. The device used for the reaction was Quant Studio 5 DX Real-Time («Applied Biosystems», USA). Amplification consisted of an initial 10-minute denaturation (95 ºC) followed by 45 cycles of amplification for 15 s (95 ºC) and for 30 s (60 °C).

Statistical analysis of the results of the study was performed using SPSS software (Statistical Package for the Social Sciences, version 17.0, IBM, USA). The value of $P < 0.05$ in all performed statistical tests was considered significant.

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Results and discussion

Distribution of alleles and genotyping by rs4977574 polymorphism of the ANRIL gene in the experimental and control groups and the results of their comparison are presented in Table 1. The first stage of statistical processing of the results was to check the distribution of allelic variants and alleles by rs4977574 polymorphic variant of the ANRIL gene in the control group and in patients with ACS according to Hardy–Weinberg and according to Table 1 this distribution corresponds to equilibrium as in the control group (p = 0.276), and in the group of patients with ACS (p = 0.058). There was a statistically significant difference in the ratio of polymorphic variants (P = 0.035), and at the same time, the distribution of A- and G-alleles SNP rs4977574 ANRIL gene in patients with ACS significantly different from those in the control group (p = 0.008).

Table 1 – Frequency of genotypes and alleles by rs4977574 ANRIL gene polymorphism in the control group and in patients with ACS

	Control group, n (%)	**Patients with ACS, n (%)**	**P**
Homozygotes A/A	78 (33.3)	50 (25.6)	0.035
Heterozygotes A/G	107 (45.8)	84 (43.1)	
Homozygotes G/G	49 (20.9)	61 (31.3)	
A-allele	263 (56.2)	184 (47.2)	0.008
G-allele	205 (43.8)	206 (52.8)	
X^2	1.186	3.591	
P_{HWE}	0.276	0.058	

Note: n – number of patients; X^2 i P_{HWE} reflect the deviations in each group from the Hardy–Weinberg equilibrium; P – statistically significant differences in the distribution of alleles and genotypes between comparison groups

Using the logistic regression method presented in Table 2, it was found that before adjusting for non-genetic risk factors, the association of rs4977574 polymorphic variant with the development of ACS was established according to recessive (P = 0.015) and additive (P = 0.012) inheritance models. Thus, homozygotes with a recessive G/G genotype are approximately 2 times more likely to develop ACS than A-allele carriers. After adjusting for the sex and age of patients, BMI, smoking habits, diabetes and stress, the identified risk remains (P = 0.049; P = 0.037 accordingly).

Table 2 – Analysis of the association of rs4977574 ANRIL gene polymorphism with the risk of ACS, taking into account different models of inheritance by logistic regression in the general group

Model	**P_{observ}**	**OR_{observ} (95% Cl)**	**P_{adjust}**	**OR_{adjust} (95% Cl)**
Dominant	0.084	1.450 (0.952–2.209)	0.214	1.351 (0.840–2.171)
Recessive	0.015	1.719 (1.110–2.660)	0.049	1.648 (1.002–2.711)
Superdominant	0.582	0.898 (0.613–1.317)	0.554	0.876 (0.565–1.358)
Additive	0.383	1.225 (0.776–1.932)	0.854	1.047 (0.645–1.700)
	0.012	1.942 (1.158–3.257)	0.037	1.792 (1.034–3.105)

Note: 95% CI – 95 % confidence interval; P_{observ} – observed value P (without adjustments for covariants); OR_{observ} – observed ratio of chances; P_{adjust} – P values after adjusting for smoking, gender, stressful occupation, diabetes and hypertension; OR_{adjust} – ratio of chances after adjustments for covariants

Among individuals with ACS and BMI < 25 kg/m^2 ratio of genotypes A/A, A/G, G/G was: 11 (32.4%), 15 (44.1%), 8 (23.5%), whereas among the control group – 25 (35.7%), 30 (42.9%), 15 (21.45) accordingly. Indicator P, calculated by Pearson's test was equal to 0.938, which indicates no difference in the distribution of genotypes among sick and healthy people (Table 3).

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The analysis of logistic regression did not reveal a difference in the risk chances in any model of inheritance both before and after the adjustments to the sex, smoking habit, the presence of diabetes, stress (Table 4).

In the group of patients with BMI >25 kg/m^2 and ACS the distribution of homozygotes by the main allele, heterozygotes and homozygotes by the minor allele was: 39 (24.2%), 69 (42.9%) and 53 (32.9%). In the group of individuals without ACS, this distribution was as follows: 53 (32.3%), 77 (47.0%) and 34 (20.7%) accordingly. Thus, the distribution of genotypes by rs4977574 polymorphic variant of the ANRIL gene is statistically significant (p = 0.035) (Table 5).

Table 3 – Association of allelic variants by rs4977574 ANRIL gene polymorphism in the control group and in patients with ACS and BMI < 25 kg/m^2

Genotype	Control group, n (%)	Patients with ACS, n (%)
Homozygotes A/A	25 (35.7)	11 (32.4)
Heterozygotes A/G	30 (42.9)	15 (44.1)
Homozygotes G/G	15 (21.4)	8 (23.5)
X^2	0.129	
P	0.938	

Note: n – number of patients; P – statistical significance

Table 4 – Analysis of the association of rs4977574 ANRIL gene polymorphism with the risk of ACS, taking into account different models of inheritance by logistic regression in the group of people with BMI < 25 kg/m^2

Model	P_{observ}	OR_{observ} (95% Cl)	P_{adjust}	OR_{adjust} (95% Cl)
Dominant	0.735	1.162 (0.487–2.770)	0.970	0.982 (0.378–2.554)
Recessive	0.809	1.128 (0.425–2.996)	0.781	1.168 (1.168–3.490)
Superdominant	0.903	1.053 (0.461–2.405)	0.793	0.885 (0.357–2.197)
Additive	0.790	1.136 (0.443–2.914)	0.881	0.924 (0.329–2.593)
	0.735	1.212 (0.398–3.690)	0.862	1.116 (0.322–3.869)

Note: 95% CI – 95% confidence interval; P_{observ} – observed value P (without adjustments for covariants); OR_{observ} – observed ratio of chances; P_{adjust} – P values after adjusting for smoking, gender, stressful occupation, diabetes and hypertension; OR_{adjust} – ratio of chances after adjustments for covariants

Table 5 – Association of allelic variants by rs4977574 ANRIL gene polymorphism in the control group and in patients with ACS and BMI > 25 kg/m^2

Genotype	Control group, n (%)	Patients with ACS, n (%)
Homozygotes A/A	53 (32.3)	39 (24.2)
Heterozygotes A/G	77 (47.0)	69 (42.9)
Homozygotes G/G	34 (20.7)	53 (32.9)
X^2	6.691	
P	0.035	

Note: n – number of patients; P – statistical significance

The method of logistic regression of allelic variants found that according to the recessive (P_{observ} = 0.014; OR_{observ} = 1.876, 95% CI = 1.137–3.095) and additive (P_{observ} = 0.014; OR_{observ} = 2.118, 95% CI = 1.166–3.849) models of inheritance, before making adjustments, carriers of G/G-genotype have a double risk to acquire ACS than those with a dominant allele. After adjustments in the corresponding models of inheritance the risk remains – recessive (P_{observ} = 0.013; OR_{observ} =

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1.951, 95% CI = 1.149–3.313) and additive (P_{observ} = 0.026; OR_{observ} = 2.039, 95% CI = 1.087–3.826) (Table 6).

lncRNA ANRIL located on the short arm of chromosome 9 (9p21.3) where it and three other protein-coding genes make up the INK4b-ARF-INK4a gene cluster, in which p14ARF, p15INK4b and p16INK4a are protein suppressors of tumors that affect cell cycle delay [21]. The known biological effects of ANRIL include its association with proliferation, apoptosis and cellular adhesion pathways [22].

Table 6 – Analysis of the association of rs4977574 ANRIL gene polymorphism with the risk of ACS, taking into account different models of inheritance by logistic regression in the group of people with BMI > 25 kg/m^2

Model	P_{observ}	OR_{observ} (95% Cl)	P_{adjust}	OR_{adjust} (95% Cl)
Dominant	0.106	1.494 (0.918–2.431)	0.237	1.363 (0.816–2.275)
Recessive	0.014	1.876 (1.137–3.095)	0.013	1.951 (1.149–3.313)
Superdominant	0.458	0.847 (0.547–1.313)	0.254	0.763 (0.479–1.215)
Additive	0.463	1.218 (0.720–2.060)	0.798	1.075 (0.617–1.875)
	0.014	2.118 (1.166–3.849)	0.026	2.039 (1.087–3.826)

Note: 95% CI – 95% confidence interval; P_{observ} – observed value P (without adjustments for covariants); OR_{observ} – observed ratio of chances; P_{adjust} – P values after adjusting for smoking, gender, stressful occupation, diabetes and hypertension; OR_{adjust} – ratio of chances after adjustments for covariants

SNP rs4977574 A/G ANRIL gene is located in the position of 103785 16th intron. The pathophysiological path of its influence on pathological processes and disease is still unknown, but the role of rs4977574 polymorphism in the development of cardiovascular diseases (CVD) has been proven by many studies around the world. Ibdah et al. in their study established the association of this polymorphism with CVD in the Jordanian population [23]. A large meta-analysis found a link between the polymorphism of rs4977574 A/G ANRIL gene in the Asian and Caucasian ethnic groups [24]. The study by Huang et al. indicates that SNP rs4977574 is a risk factor for ACS among women in the Asian population [25]. However, when studying the association of the Chinese population with BMI < 24 kg/m^2 and > 24 kg/m^2 and rs4977574, no significant difference in the distribution of genotypes was found [26].

It should be noted that studies that would establish a link between the rs4977574-polymorphic variant of the ANRIL gene and other risk factors are currently insufficient to accurately establish the role of this polymorphism.

CONCLUSIONS/ВИСНОВКИ

1. There is a significant difference in the distribution of genotypes A/A, A/G, G/G by rs4977574 ANRIL gene polymorphism among ACS patients and control group.
2. Recessive G/G genotype homozygotes are approximately 2 times more likely to develop ACS than A-allele carriers. After adjusting for the sex and age of patients, BMI, smoking habits, diabetes and stress, the identified risk remains.
3. The distribution of genotypes according to SNP rs4977574 of the ANRIL gene in the group of patients with ACS and the control group among individuals with and BMI <25 kg/m2 does not differ.
4. Among patients with BMI>25 kg/m2, the distribution of genotypes by rs4977574 polymorphic variant of the ANRIL gene is statistically significant.
5. Individuals with a BMI>25 kg/m2 who are carriers of the G/G genotype have a double risk of developing ACS than individuals with a dominant allele.

PROSPECTS FOR FUTURE RESEARCH/ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Further research will be aimed on studying the impact of ANRIL polymorphism upon the risk of ACS development depending on other risk factors.

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CONFLICT OF INTEREST/КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS/ЗВ'ЯЗОК РОБОТИ З НАУКОВИМИ ПРОГРАМАМИ

The study was conducted as the scientific thesis research of the department of the Department of Physiology and Pathophysiology with a course in medical biology: "Study of the role of genetic factors in the pathogenesis of multifactorial diseases", state registration №0120U102166.

FUNDING/ДЖЕРЕЛА ФІНАНСУВАННЯ

None.

AUTHOR CONTRIBUTIONS/ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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(received 20.06.2022, accepted 28.06.2022)

(одержано 20.06.2022, затверджено 28.06.2022)

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