ASSOCIAÇÃO DO ALELO DELEÇÃO DA INSERÇÃO / DELEÇÃO POLIMORFISMO DO AIBB3 INTEGRINA GENE E SÍNDROME METABÓLICA EM NORTISTAS JOVENS**ASSOCIATION OF THE DELETION ALLELE OF THE INSERTION/DELETION POLYMORPHISM OF *allbβ3* INTEGRIN GENE AND METABOLIC SYNDROME IN YOUNG NORTHERNERS****АССОЦИАЦИЯ ДЕЛЕЦИОННОГО АЛЛЕЛЯ ПОЛИМОРФИЗМА ВСТАВКИ / ДЕЛЕЦИИ ГЕНА *allbβ3* ИНТЕГРИНА И МЕТАБОЛИЧЕСКОГО СИНДРОМА У МОЛОДЫХ ЖИТЕЛЕЙ СЕВЕРА**

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RESUMO

A justificativa para o presente estudo é explicada por uma alta disseminação da síndrome metabólica entre a população jovem, que é um dos principais fatores de risco cardiovascular. O estudo visa investigar a associação entre um alelo de deleção do polimorfismo de deleção/inserção no gene da integrina *allbβ3* e síndrome metabólica em os jovens do norte. Foram examinados 758 jovens de 18 a 44 anos (idade média de 36,62 ± 5,12 anos) com síndrome metabólica e 77 jovens saudáveis e sem distúrbios metabólicos. A transportadora do alelo I associado ao risco cardiovascular foi revelada em 63% dos pacientes examinados que apresentaram risco aumentado de desenvolvimento de distúrbios metabólicos (OR 1,409, IC 95% 0,858-2,311, p = 0,253). Não houve diferença significativa entre as populações nativas e não nativas na taxa de ocorrência do alelo I (62,2% e 64,7%). O genótipo II teve associação significativa com hipertensão arterial (OR 1,377, IC 95% 0,912-2,080, p = 0,073), obesidade (OR 1,335, IC 95% 0,825-2,219, p = 0,071), hipercolesterinemia (OR 1,386, IC 95% 0,977 -1,966, p = 0,115), hipertrigliceridemia (OR 1,232, IC 95% 0,889-1,706, p = 0,097). Foi estabelecido que a população não nativa apresentava maior risco de desenvolvimento de obesidade abdominal, hipertensão arterial e hipercolesterinemia, diferentemente da população nativa que apresentava risco significativamente maior de desenvolvimento de trigliceridemia. Os materiais do artigo podem ser úteis para a avaliação da predisposição genética ao infarto do miocárdio, acidente vascular cerebral e tromboembolismo, o que permitirá a indicação oportuna de medidas preventivas.

Palavras-chave: *gene da integrina allbβ3, síndrome metabólica, obesidade, hipertensão arterial, hipercolesterolemia, hiperglicemia.*

ABSTRACT

The rationale for the present study is explained by a high spread of metabolic syndrome among the young population, living in an area equivalent to the Far North. The study is aimed at the investigation of the association between a deletion allele of the polymorphism of deletion/insertion in the *allbβ3* integrin gene and metabolic syndrome in young residents Khanty-Mansiysk Autonomous Okrug – Ugra (Russia). The 758 young people aged 18-44 (mean age 36.62±5.12 years old) with metabolic syndrome and 77 healthy young people without metabolic disorders were examined. The carriership of the allele I associated with the cardiovascular risk was revealed in 63% of the examined patients that had an increased risk of the development of metabolic disorders (OR 1.409, 95% CI 0.858-2.311, p=0.253). There was no significant difference between the native and non-native populations in the rate of occurrence of allele I (62.2% and 64.7%). Genotype II had significant

association with arterial hypertension (OR 1.377, 95 % CI 0.912-2.080, $p=0.073$), obesity (OR 1.353, 95% CI 0.825-2.219, $p=0.071$), hypercholesterinemia (OR 1.386, 95% CI 0.977-1.966, $p=0.115$), hypertriglyceridemia (OR 1.232, 95% CI 0.889-1.706, $p=0.097$). It was established that the non-native population had a higher risk of the development of abdominal obesity, arterial hypertension, and hypercholesterinemia, unlike the native population that had a significantly higher risk of the development of triglyceridemia. The materials of the article can be useful for the evaluation of genetic predisposition to myocardial infarction, stroke, and thromboembolism, which will allow for timely indication of preventive measures.

Keywords: *allb β 3 integrin gene, metabolic syndrome, obesity, arterial hypertension, hypercholesterolemia, hyperglycemia.*

АННОТАЦИЯ

Актуальность исследования обусловлена высоким распространением в настоящее время метаболическим синдромом среди молодого населения, проживающих в местности, приравненной к Крайнему Северу. В связи с этим, данная статья направлена на изучение ассоциации делеционного аллеля полиморфизма вставки / делеции в гене α IIb β 3 интегрина и метаболического синдрома у молодых жителей Ханты-Мансийского автономного округа - Югры. Было обследовано 758 молодых человека в возрасте 18-44 года (средний возраст $36,62 \pm 5,12$ лет) с проявлениями метаболического синдрома и 77 здоровых молодых людей без метаболических нарушений. Установлено, что носительство аллеля I, связанного с кардиоваскулярным риском, было выявлено у 63% всех обследованных, имевших повышенный риск развития метаболических нарушений (ОШ 1.409, 95% ДИ 0.858-2.311, $p=0.253$). Среди некоренных и коренных жителей по частоте носительства аллеля I достоверных различий не выявлено – 62,2 % и 64,7 %. Генотип II показал значительную ассоциацию с артериальной гипертензией (ОШ 1.377, 95 % ДИ 0.912-2.080, $p=0.073$), ожирением (ОШ 1.353, 95% ДИ 0.825-2.219, $p=0.071$), с гиперхолестеринемией (ОШ 1.386, 95% ДИ 0.977-1.966, $p=0.115$), с гипертриглицеридемией (ОШ 1.232, 95% ДИ 0.889-1.706, $p=0.097$). Среди некоренного населения установлено увеличение шансов развития абдоминального ожирения, артериальной гипертензии, гиперхолестеринемией, в отличие от коренных жителей, у которых определено высоко отношение шансов развития триглицеридемии. Материалы статьи представляют практическую ценность для оценки генетической предрасположенности к инфаркту миокарда, инсульту, тромбоэмболии, что позволит своевременному проведению профилактических мероприятий.

Ключевые слова: *ген α IIb β 3 интегрин, метаболический синдром, ожирение, артериальная гипертензия, гиперхолестеринемия, гиперликемия.*

1. INTRODUCTION

It is known that metabolic syndrome, in particular, such components as obesity and insulin resistance, are closely associated with the disorders in the systems of coagulation and fibrinolysis, which leads to the increase in the risk of the development of cardiovascular diseases (Berkovskaya and Butrova, 2009). In patients with obesity, the hyperactivity of thrombocytes, as the main component of metabolic syndrome, is a pathogenetic factor of atherotrombogenesis, which is manifested as an increased adhesion and a capability to aggregate. Such activity of platelets can be associated with the damage of platelet membranes, increased expression of the superficial receptors for the molecules of adhesion, failure of intracellular metabolic processes inside the cells (Boden, 2008; Chromylev, 2015). Platelets aggregate due to the presence of receptors (protein-integrin complexes) located on their surface.

A possible association of different polymorphisms in the integrin gene and thromboembolic complications are described by numerous authors (Kokubo *et al.*, 2007). Integrins are transmembrane glycoproteins that are involved in the intercellular and cellular-matrix interactions and consist of α - and β -subunits. The most widespread is α IIb β 3 integrin that is located on the long arm on the 17th chromosome in the locus 17q21.32 and expressed on the surface of thrombocytes being a receptor of fibrinogen (Calvete, 1995; Westerbacka *et al.*, 2002; Chernyak and Snezhitskiy, 2018). Trombocytopathias can develop as a result of a mutation in the genes α IIb β 3 (Huang *et al.*, 2019).

The study was aimed to investigate the associations between a deletion allele of polymorphism of insertion/deletion in the α IIb β 3 integrin gene and metabolic syndrome in young northerners.

2. MATERIALS AND METHODS

The study was performed in the facilities of Fedorovskaya municipal clinical hospital, the branch of the hospital in vil. Russkinskaya and Surgutskaya municipal clinical hospital №1. 758 young people aged 18-44 (mean age 36.62 ± 5.12 years old) with metabolic syndrome and 77 healthy young people without metabolic disorders were examined. The non-native population was represented by urban and rural populations. The native northern population was represented by Khanty and Mansi. The main criterion for the metabolic syndrome was an increase in the waist measurement to more than 94 cm in men and more than 80 cm in women (Ferreira *et al.*, 2005). Additional criteria were arterial hypertension (AH $\geq 130/85$ mmHg), an increase in the level of triglycerides (TG) (≥ 1.7 mmol/L), a decrease in the level of cholesterol HDL (<1.0 mmol/L in men; <1.2 mmol/L in women), an increase in the level of cholesterol LDL > 3.0 mmol/L, hyperglycemia before meal (glucose in plasma before meal ≥ 6.1 mmol/L), glucose intolerance (glucose in plasma 2 hours after the exposure within the range of ≥ 7.8 and ≤ 11.1 mmol/L) (Russian Society of Cardiology, 2009). The state of lipid and carbohydrate metabolism was evaluated in blood plasma taken from the fasting ulnar vein from them at least 12 hours after the last meal. The content of blood lipids was determined on a biochemical express analyzer Reflotron Plus (Roche Diagnostics, Switzerland).

The content of LDL cholesterol was evaluated using the Friedwald formula at a TG concentration below 4.5 mmol / L: LDL cholesterol = total cholesterol - (HDL cholesterol + TG / 2.2), mmol / L. An oral glucose tolerance test (PTTG) was performed with a load of 75 g glucose. In the morning, after complete fasting for 8-14 hours, blood was taken from the cubital vein from the subjects to determine plasma glucose. 15 minutes before the study, the patients were in a calm state, in a comfortable sitting position. Then they drank 75 g of glucose dissolved in 250-300 ml of water in 5 min. After 2 h, blood was again taken from the peripheral vein, and the plasma glucose level was determined.

The characteristics of the examined patients are presented in Table 1. All the participants underwent anthropometric examination (height, body weight, body mass index ($BMI = kg/m^2$), waist measurement (WM), blood pressure, total cholesterol, HDL, LDL, triglycerides, carbohydrate metabolism). The molecular-genetic study was performed in the Department of the Federal State Budgetary

Scientific Institution "Federal Research Center Institute of Cytology and Genetics of the Siberian Department of the Russian Academy of Sciences. Genome DNA was isolated from venous blood by the method of phenol-chloroform extraction. Polymorphism of *α11bβ3* integrin was tested with polymerase chain reaction (PCR) with restriction fragment length polymorphism (RFLP).

All the patients signed the form of informed consent for participation in the study. The present study was approved by the Expert Council of the Surgut State University.

The obtained results were processed statistically with a software package SPSS 16.0. The authors estimated the frequency rate of genotypes of the studied single nucleotide polymorphism (SNP) in the ethnic groups with metabolic syndrome and in the control group. The comparison of groups by the frequency rate of genotypes was performed with cross tables using Pearson's chi-square test with the calculation of the error of the mean (m) and mean value (M). In the case of the fourfold table, a two-tailed Fisher-Yates test was applied. The relative risk of the development of the components of metabolic syndrome for a certain allele or genotype was calculated as odds ratio (OR). Confidential interval (CI) was calculated by two-tailed Fisher's test and Pearson's chi-square test. The data was significant at $p < 0.05$.

Table 1. Characteristics of the examined patients with MS, ($M \pm m$)

Parameters	Values
Bodyweight, kg	83.52 ± 0.03
BMI, kg/m^2	32.07 ± 0.49
Waist measurement, cm	91.39 ± 0.85
Glucose level before a meal, mmol/L	5.47 ± 0.55
Glucose level 2 hours after the exposure, mmol/L	6.52 ± 0.012
Total cholesterol, mmol/L	5.47 ± 0.63
Triglycerides, mmol/L	2.54 ± 0.15
HDL mmol/L	1.69 ± 0.16
LDL, mmol/L	3.08 ± 0.011
SBP, mmHg	115.52 ± 0.04
DBP, mmHg	75.29 ± 0.03

3. RESULTS AND DISCUSSION

The spread of genotypes and alleles of the integrin gene *α11bβ3* among the studied native and non-native populations is presented in Table

2. The frequency rate of the carriership of the genotype DD was 14.4%, ID – 45.2%, II – 40.4%. The carriership of the allele I associated with the risk of the development of cardio-vascular diseases was revealed in 63% of the examined patients. There was no significant difference between native and non-native populations by the frequency rate of the carriership of the allele I (62.2% and 64.7%, respectively) (Table 2).

In the group of the native population with metabolic syndrome, the frequency rate of the carriership of genotype II of insertion and deletion polymorphism of *αIIbβ3* integrin gene was 64.9%, and in a certain part of the non-native population with metabolic disorders – 60.5%. In the control group of the native population, the carriership of the genome II was observed by 6.9% more often than in the control group of the non-native population. The frequency rate of the carriership of the genotype II among the non-native population with metabolic syndrome was higher than in the control group (60.5% and 54.2%, respectively). Among the native population, the frequency rate of carriership of the genotype II in patients with metabolic syndrome and the control group was not statistically significant (64.9% and 61.1%, respectively). It was established that the carriers of the allele II of *αIIbβ3* integrin gene had an increased risk of the development of metabolic disorders (OR 1.409, 95% CI 0.858-2.311, $p=0.253$) (Table 3).

Table 4 shows the results of the study of the association between polymorphisms of *αIIbβ3* gene integrin and the components of metabolic syndrome. Thus, there was a significant association between genotype II and high blood pressure (OR 1.377, 95% CI 0.912-2.080, $p=0.073$), high BMI (OR 1.353, 95% CI 0.825-2.219, $p=0.071$), hypercholesterinemia (OR 1.386, 95% CI 0.977-1.966, $p=0.115$), hypertriglyceridemia (OR 1.232, 95% CI 0.889-1.706, $p=0.097$) (Table 4).

Figure 1 contains the data on the revealed association of polymorphism of *αIIbβ3* integrin gene with metabolic syndrome among native and non-native young populations. Non-native population had a higher OR of the development of abdominal obesity (OR 1.418, 95% CI 0.797-2.522, $p=0.294$), arterial hypertension (OR 1.661, 95% CI 1.016-2.714, $p=0.251$), hypercholesterinemia (OR 1.612, 95% CI 1.043-2.492, $p=0.222$) unlike native population that had a high OR of the development of triglyceridemia (OR 1.508, 95% CI 0.846-2.688, $p=0.295$).

The present study was conducted for the investigation of the role of deletion allele of the

polymorphism of insertion/deletion in *αIIbβ3* integrin gene in young northerners with metabolic syndrome.

Different authors in their works showed the allele of the deletion II of the *αIIbβ3* integrin gene was associated with unfavorable metabolic and vascular effects (Amabile *et al.*, 2014). Thus, the Czech authors showed a positive correlation between the expression of *αIIbβ3* integrin and hyperglycemia before a meal ($r=0.48$, $p<0.05$) (Osmancik *et al.*, 2007). Patients with insulin resistance have a high risk of the development of thrombosis. It was proved experimentally that the removal of the insulin receptor from the surface of a platelet led to an increase in the platelet count, but the influence of insulin on them was blocked. In platelets that did not have insulin receptors, it was established that the aggregation of platelets and the enhancement of the activation of *αIIbβ3* integrin were reduced (Moore *et al.*, 2015). It is known that insulin resistance has a genetic background. A high risk of the development of diabetes mellitus type II in 506 patients with disturbances of tolerance to glucose (OR = 5.17, 95% CI 1.76-15.21, $p=0.003$) was revealed in comparison with patients that changed their lifestyle (Siitonen *et al.*, 2004).

An association between polymorphism of insertion/deletion (I/D) *αIIbβ3* and arterial hypertension in patients with diabetes mellitus and without it was established. The rate of frequency of the genotype DD was significantly higher both in patients with arterial hypertension with diabetes (77.14%, $p<0.01$) and without it (71.43%, $p<0.05$) in comparison with the control (40%). Besides, allele D was more often observed in patients with hypertonic disease and diabetes (84.29%, $p<0.01$) and without it (80%, $p<0.05$) in comparison with control (58.33%). At the same time, it was revealed that genotype DD was associated with a low level of HDL ($p=0.001$) and a high level of LDL ($p=0.017$) in comparison with genotypes II and ID in the group of patients with arterial hypertension and without diabetes mellitus type II (Tayel *et al.*, 2012). It was established that functions of platelets and activation of *αIIbβ3*, caused by thrombin, decrease in patients with obesity. A decrease in the activity of sarcoendoplasmic net Ca^{2+} + ATPase (SERCA3) by 48% is also observed. The loss of weight restores the activity of SERCA3 and further transmission of calcium signals, activation of *αIIbβ3*, aggregation of platelets, and secretion of ADP (Elaib *et al.*, 2019).

On the other hand, some data prove the involvement of insulin in the regulation of the activation of platelets. Thus, in people with

normal body weight, insulin can inhibit the aggregation of platelets, unlike in people with obesity that do not have insulin to exert this function, which can contribute to further damage of the vascular wall (Kohler, 2002; Westerbacka *et al.*, 2002). It was established that higher activity of platelets was observed in patients with a more severe degree of ischemic heart disease (Osmancik *et al.*, 2007). In many works, the association between a mutant allele I in *αIIbβ3* integrin gene and the development of myocardial infarction, ischemic heart disease, and thromboembolism was established, especially at a younger age (Chernyak and Snezhitskiy, 2018; Aksyutina *et al.*, 2013; Ali Elsidege *et al.*, 2019; Xu *et al.*, 2014).

4. CONCLUSION

Thus, in our study, we obtained a significant association of the polymorphism of insertion/deletion in the *αIIbβ3* integrin gene with metabolic disorders among young indigenous and non-indigenous patients of the Khanty-Mansiysk Autonomous Okrug-Ugra. Carriage of the allele I, associated with the risk of developing cardiovascular diseases, was observed in 63% of all examined patients with metabolic disorders. In our study, genotype II showed a significant association with arterial hypertension (OR 1.661), obesity (OR 1.418) and hypercholesterolemia (OR 1.612) in young non-indigenous people of the North, in contrast to the indigenous people, who have a high ratio of the chances of triglyceridemia (OR 1.508). The identification of the genotype *αIIbβ3* integrin allows for an evaluation of genetic predisposition of young northerners to myocardial infarction, stroke, and thromboembolism, and timely indication of preventive measures.

5. LIST OF ABBREVIATIONS

AO – abdominal obesity,
AH – arterial hypertension,
HCL - hypercholesterolemia,
HCL - hypertriglyceridemia,
HG – hyperglycemia.

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TABLES

Table 2. The rate of occurrence of insertion and deletion polymorphism of gene *allbβ3* in ethnical groups.

Population	The rate of occurrence of genotypes						The rate of occurrence of alleles			
	DD		ID		II		D		I	
	n	%	n	%	n	%	n	%	n	%
Non-native population (n=569)	93	16.3	255	44.8	221	38.8	441	38.8	697	61.2
Native population (n=266)	33	12.4	122	45.9	111	41.7	188	35.3	344	64.7
Total	126	14.4	377	45.2	355	40.4	649	37	1107	63

Table 3. The rate of frequency of insertion and deletion polymorphism of *allbβ3* integrin gene in the studied groups

Genotype	Control group, n=77		Patients with metabolic syndrome, n=758		OR, 95% CI, p
	n	%	n	%	
Total, n=835					
DD	17	22.1	117	15.4	0.644, 0.363-1.143, p=0.293
ID	34	44.2	343	45.3	1.045, 0.652-1.676, p=0.241
II	26	33.8	298	39.3	1.409, 0.858-2.311, p=0.253
Allele D	68	44.2	577	38.1	0.777, 0.556-1.086, p=0.171
Allele I	86	55.8	939	61.9	1.287, 0.921-1.798, p=0.171
Non-native population, n=569					
DD	14	23.7	87	17.1	0.631, 0.332-1.200, p=0.328
ID	26	44.1	229	44.9	1.034, 0.601-1.780, p=0.277
II	19	32.2	194	38.0	1.292, 0.728-2.296, p=0.293
Allele D	54	45.8	403	39.5	0.774, 0.528-1.136, p=0.196
Allele I	64	54.2	617	60.5	1.292, 0.880-1.895, p=0.196
The native population, n=266					
DD	3	16.7	30	12.1	0.688, 0.188-2.517, p=0.138
ID	8	44.4	114	46.0	1.063, 0.406-2.785,p=0.491
II	7	38.9	104	41.9	1.135, 0.426-3.026, p=0.500
Allele D	14	38.9	174	35.1	0.849, 0.424-1.701, p=0.355
Allele I	22	61.1	322	64.9	1.178, 0.588-2.360, p=0.355

Table 4. Association between homozygotic II polymorphism of *allbβ3* integrin and parameters of metabolic syndrome in the studied groups

Parameter	DD n (%)		ID n (%)		II n (%)		OR, 95% CI, p	
Abdominal Obesity (AO)								
Patients with AO	109	14.9	323	44.2	298	40.8	1.353, CI 0.825-	2.219, p=0.071
Patients without AO	17	22.1	34	44.2	26	33.8		
Arterial Hypertension (AH)								
Patients with AH	15	14.2	49	46.2	42	39.6	1.377, CI 0.912-	2.080, p=0.073
Patients without AH	290	31.9	328	36.2	290	31.9		
Hypercholesterolemia (HCL)								
Patients with HCL	93	12.8	249	53.3	243	33.9	1.386, CI 0.977-	1.966, p=0.115
Patients without HCL	23	12.8	96	53.3	61	33.9		
Hypertriglyceridemia (HTG)								
Patients with HTG	26	13.1	87	43.9	85	42.9	1.232, 0.889-1.706,	p=0.097
Patients without HTG	98	16.2	277	46.9	229	37.9		
Hyperglycemia (HG)								
Patients with HG	35	13.0	135	50.0	100	37.0	0.812, 0.604-1.092,	p=0.050
Patients without HG	92	15.6	249	42.3	247	42.1		

Note: AO – abdominal obesity, AH – arterial hypertension, HCL - hypercholesterolemia, HTG - hypertriglyceridemia, HG – hyperglycemia. $p < 0.05$

FIGURES

Note: AO – abdominal obesity, AH – arterial hypertension, HCL - hypercholesterolemia, HTG - hypertriglyceridemia, HG – hyperglycemia. $p < 0.05$

Figure 1. OR of the frequency rate of homozygotic II polymorphism *allbβ3* with the parameters of metabolic syndrome in the studied ethnic groups.