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THE ROLE OF THE COMBINATIONS OF GENES POLYMORPHISMS OF THE BETA 1- AND BETA 3 ADRENERGIC RECEPTORS IN A HEART VASCULAR DISEASES AND DIABETES MELLITUS TYPE 2

Abstract: *In this article we studied clinical metabolic determinants depending on the genes polymorphism combinations of beta 1- and beta 3 adrenergic receptors.*

Key words: *gene polymorphism, beta 1- and beta 3 adrenergic receptors, clinical and metabolic determinants.*

Language: *English*

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BACKGROUND: The main role in developing of heart vascular diseases (HVD) and diabetes mellitus type 2 acts genes [1]. Many studies have discussed genes which are responsible for evolution HVD and diabetes mellitus type 2 [2-4]. Similar researches were performed in Kazakhstan [5-8].

Nowadays is determined that genes polymorphism combinations have impact on the development of HVD and diabetes mellitus type 2. Researchers from Chile studying the link between the gene polymorphism combinations of beta 1 (ADRB1) and beta 3 adrenergic receptors (ADRB3) with sudden death, determined that people with ADRB1Arg389Gly and ADRB2 Gln27Glu gene polymorphisms combinations have a high risk of sudden death [9]. The aim of the Polish scientists was to study the association of polymorphisms gene between beta 1 adrenergic receptors (Ser49Gly, Arg389Gly) and beta 2 adrenergic receptors (Arg16Gly, Gln27Glu, Thr164Ile) with idiopathic dilated cardiomyopathy. The results showing that, beta-adrenergic receptor polymorphisms did not seem to play a significant role in IDCM in the Polish population. [10]. There was also determined the association of gene polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg389Gly and Trp64Arg with the evaluating of metabolic changes of the patients with diabetes mellitus type 2 and metabolic syndrome [11].

AIM: To study combinations of the genes polymorphism of beta 1 and beta 3 adrenergic receptors depending on clinical metabolic and death rates.

DESIGN: We conducted this as a retrospective cohort study.

MATERIAL AND METHODS: We took the initial material of Shalkharova Zh.S., 2003 [12], Nuskabaeva G.O., 2003[7], Askarova S.S., 2003 [13] and were able to examine 130 patients with the gene polymorphism combinations of beta 1 and beta 3 adrenergic receptor**s,** which were included further in our research. From whole 130 people 21 were deaths. We investigated 109 alive patients, whose mean age was 57,42±13,34. All patients, which were included in our study gave their agreement to participate in it. They were divided into 5 groups, depending on the genes of polymorphism combinations of beta 1 and beta 3 adrenergic receptors**:**

1. Arg/Arg+Trg/Trg – 66 volunteers – 50,8%
2. Arg/Arg+Trg/Arg – 21 volunteers – 16,1%
3. Arg/Gly+Trg/Trg – 30 volunteers – 23,1%
4. Arg/Gly +Trg/Arg – 10 volunteers – 7,7%
5. Arg/Arg+ Arg/Arg – 3 volunteers – 2,3%

We made analysis by the next determinants:

1. Clinical antropometric: weight, height, waist (WC) and thigh circumstances, body mass index (BMI)

2. Biochemic analyses: glucose level of blood (norm is 3.89-5.6 mmol/l), total cholesterol (norm 3.3-5.0 mmol/l), HDL cholesterol (norm for men ≥ 1.0, for women ≥ 1.20 mmol/l), triglycerides (norm < 1.70 mmol/l). LDL cholesterol was claimed by Friedewald W.T. [14]: LDL cholesterol= Total cholesterol - HDL cholesterol- Triglycerides/2,2.

Molecular genetic analysis of genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors examined 12 years ago in a laboratory of human being genome by Scientific Research Institute of molecular biology and genetics of plants in the Republic of Uzbekistan under the direction of doctor of medicine, prof. Mukhamedov R.S. [13].

Statistical analysis was made using MS EXCEL, Biostat software.

RESULTS: By the results of our study from 130 volunteers 21 were dead by the time of the research (Table 1). In the group with the genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Trg died 14 respondents (21.2%), Arg/Arg+Trg/Arg – 1 respondents (4.8%), Arg/Gly+Trg/Trg – 4 respondents (13.3%), Arg/Gly+Trg/Arg – 2 respondents (20%), consequently.

Table 1

Distribution of deaths by the genes **polymorphism combinations of beta 1- and beta 3 adrenergic receptors.**

Genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors	Arg/Arg+ Trg/Trg		Arg/Arg+ Trg/Arg		Arg/Gly+ Trg/Trg		Arg/Gly+ Trg/Arg	
	n	%	N	%	n	%	n	%
Total	66	100%	24	100%	30	100%	10	100%
Death	14	21,2%	1	4,1%	4	13,3%	2	20,0%

Acute stroke was statistically significantly frequently founded by distributing the causes of death (42.1%). And 12.1% of people with genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Trg died with acute stroke (Table 2).

Table 2

Causes of death of patients with the genes polymorphism combinations of beta 1- and beta 3 adrenergic receptors.

Gene polymorphism combinations of beta 1 and beta 3 adrenergic receptors	Arg/Arg+ Trg/Trg		Arg/Arg+Trg/Arg		Arg/Gly+Trg/Trg		Arg/Gly+ Trg/Arg	
	n	%	N	%	n	%	n	%
Acute cerebrovascular accident	8	12,1%			3	10,0%	2	20,0%
Ischemic heart disease	1	1,5%	1	4,8%				
Diabetes mellitus type 2	1	1,5%						
Other causes	4	6,1%			1	3,3%		
Total	14	21,2%	1	4,8%	4	13,3%	2	20,0%
	χ^2 =11,792 p=0,01							

Thus, analyzing the results by deaths with depending the gene polymorphism combinations of beta 1 and beta 3 adrenergic receptors, we can say that people the gene polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Trg were founded more frequently, than other combinations. The proportion of deaths less met with a combination of polymorphisms beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Arg. Based on the data obtained by us can be divided into combination of polymorphisms of beta 1 and beta 3 adrenergic receptors on the «favorable» (Arg/Arg+Trg/Arg) and «non-favorable» (Arg/Arg+Trg/Trg, Arg/Gly+Trg/Trg, Arg/Gly+Trg/Arg) combinations of polymorphisms of genes. With «non-favorable» combinations of polymorphisms genes beta 1 and beta 3 adrenergic receptors most frequent cause of death was acute cerebrovascular accident (CVA).

Studying in alive patients anthropometric and biochemic parameters, we identified key differences by genes polymorphism. It was examined average clinical metabolic figures in the contrast with the 2003 year's parameters by the genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors. Looking each combinations of the genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors individually we took statistically significant changes of such determinants as BMI, WC, triglycerides and glucose values in people with «non-favorable» combinations Arg/Arg+Trg/Trg (Table 3). But there were no statistically significantly differences in patients with genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Arg (Table 4) and Arg/Gly+Trg/Trg (Table 5). Volunteers with the genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Gly+Trg/Arg (Table 6) and Arg/Arg+Trg/Trg had statistically significant p-value changes in BMI and WC.

Table 3

12-year developing metabolic risk factors depending on the genes polymorphism combinations of beta 1- and beta 3 adrenergic receptors Arg/Arg+Trg/Trg.

Indicators	Arg/Arg+Trg/Trg M(SD)		P
	2003	2015	
BMI, kg/m^2	26,29±5,68	29,3±5,65	0,002
WC, m	87,84±13,64	95,22±14,33	0,001
total cholesterol, mmol/l	5,19±0,96	5,33±1,07	0,296
HDL, mmol/l	1,2±0,31	1,33±0,35	0,032
Triglycerides, mmol/l	1,46±0,43	1,73±0,96	0,043
LDL, mmol/l	3,34±0,97	3,25±0,77	0,586
Glucose, mmol/l	5,61±2,07	6,43±3,01	0,000
Systolic blood pressure, mmHg	132,5±25,52	133,5±23,86	0,838
Diastolic blood pressure, mmHg	84,5±12,13	84,2±11,57	1,000

Table 4

12-year developing metabolic risk factors depending on the genes polymorphism combinations of beta 1- and beta 3 adrenergic receptors Arg/Arg+Trg/Arg.

Indicators	Arg/ Arg+Trg/ Arg M(SD)		P
	2003	2015	
BMI, kg/m^2	27,31±5,00	29,2±6,07	0,282
WC, m	89,77±14,74	95,11±9,51	0,176
total cholesterol, mmol/l	5,14±0,8	5,69±1,1	0,074
HDL, mmol/l	1,18±0,22	1,29±0,38	0,261
Triglycerides, mmol/l	1,55±0,52	1,5±0,52	0,760
LDL, mmol/l	3,26±0,78	3,62±1,27	0,276
Glucose, mmol/l	5,78±1,85	5,77±1,22	0,984
Systolic blood pressure, mmHg	124,7±23,54	128,61±24,6	0,586
Diastolic blood pressure, mmHg	81,66±12,83	83,88±9,78	0,551

Table 5

12-year developing metabolic risk factors depending on the genes polymorphism combinations of beta 1- and beta 3 adrenergic receptors Arg/Gly+Trg/Trg.

Indicators	Arg/Gly+Trg/Trg M(SD)		P
	2003	2015	
BMI, kg/m	27,73±7,13	29,51±6,032	0,260
WC, m	95,21±18,77	98,04±13,28	0,506
total cholesterol, mmol/l	5,17±1,1	5,35±0,88	0,361
HDL, mmol/l	1,2±0,32	1,29±0,41	0,304
Triglycerides, mmol/l	1,59±0,41	1,65±0,6	0,660
LDL, mmol/l	3,25±1,31	3,22±0,79	0,919
Glucose, mmol/l	7,16±5,14	7,03±3,25	0,917
Systolic blood pressure, mmHg	136,08±20,39	136,30±27,22	0,947
Diastolic blood pressure, mmHg	87,82±12,77	86,08±13,39	0,406

Table 6

12-year developing metabolic risk factors depending on the genes polymorphism combinations of beta 1- and beta 3 adrenergic receptors Arg/Gly+Trg/Arg.

Indicators	Arg/Gly+Trg/Arg M(SD)		P
	2003	2015	
BMI, kg/m^2	26,12±4,28	29,41±2,14	0,05
WC, m	91,12±8,67	97,62±8,76	0,007
total cholesterol, mmol/l	5,35±0,73	5,03±0,9	0,416
HDL, mmol/l	1,1±0,21	1,03±0,24	0,519
Triglycerides, mmol/l	1,62±0,63	2,07±0,99	0,257
LDL, mmol/l	3,51±0,75	2,86±0,64	0,069
Glucose, mmol/l	5,6±2,87	6,25±1,77	0,584
Systolic blood pressure, mmHg	121,25±13,56	123,75±7,3	0,701
Diastolic blood pressure, mmHg	77,5±7,07	78,75±12,46	0,791

There were statistically significant p-value changes in BMI and WC in people with HVD and diabetes, depending on genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Trg and Arg/Gly+Trg/Arg (Table 7).

Table 7

Average values of WC and BMI in people with HVD and diabetes mellitus type 2 by the genes polymorphism combinations of beta 1- and beta 3 adrenergic receptors

genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors	Arg/Arg+Trg/Trg		Arg/Arg+Trg/Arg		Arg/Gly+Trg/Trg		Arg/Gly+Trg/Arg	
Indicators	2003	2015	2003	2015	2003	2015	2003	2015
WC	91,8±15,3	112,0±9,2	99,7±6,4	101,5±12,2	101,2±16,1	102,8±15,9	95,4±5,9	103,2±5,1
	p=0,014		p=0,634		p=0,410		p=0,0015	
BMI	27,9±7,1	35,6±3,1	29,9±1,0	30,9±2,7	30,4±5,7	30,9±7,6	28,9±3,6	32,1±6,3
	p=0,014		p=0,475		p=0,935		p=0,353	

CONCLUSION:

The genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors acts in HVD and diabetes mellitus type 2 [11].

The genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors were divided into two groups: “favourable” and “non-favourable”.

The genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Trg were founded more frequently, than other combinations. The least proportion of deaths were people with the genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Arg and the most proportion contained people with the gene polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Trg. Among all causes of death acute stroke statistically significant founds more frequently than others.

“Non-favourable” genes polymorphism combinations of beta 1 and beta 3 adrenergic receptors were Arg/Arg+Trg/Trg and Arg/Gly+Trg/Arg, because of their predictors such classic factors as obesity, hyperglycemia, hypertriglyceridemia, which raise the risk of HVD and diabetes mellitus type 2. In patients with HVD and diabetes mellitus type 2 were determined changes with the gene polymorphism combinations of beta 1 and beta 3 adrenergic receptors Arg/Arg+Trg/Trg и Arg/Gly + Trg/Arg.

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