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Study of Genes Predisposition to The Development of Complications of Metabolic Syndrome

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ABSTRACT

This review presents the most informative genes for the diagnosis of complications of metabolic syndrome. It is shown that the polymorphism G-455A (rs1800790) of the gene FGB, Glu298Asp (rs1799983) of the gene eNOS, G83A (rs2368564) of the gene REN are the most informative markers to as-sess the possibility of fatal complications of metabolic syndrome. Risk assessment and prognosis of the disease course is multifactorial, where the most formative method will be the assessment of the complex of many single-nucleotide polymorphisms of genes, since the presence of a synergistic interac-tion of genetic polymorphisms is important, when the presence of unfavorable variants of genes of several systems increases the probability of the disease and its more severe course.

Keywords

Metabolic syndrome, Gene identification of complications.

Introduction

The prevalence of metabolic syndrome (MS), which is a complex of pathogenically interrelated metabolic disorders - abdominal obesity, increased blood pressure, insulin resistance, dyslipidemia, according to a number of large epidemiological studies range from 20 to 45% [1]. With the development of MS, there is a 5-fold increase in the risk of type 2 diabetes and a 2-fold increase in the risk of developing cardiovascular diseases over the next 5-10 years. In addition, in patients with MS, the risk of stroke increases by 2-4 times, by 3-4 times myocardial infarction, the risk of death from these diseases increases by 2 times compared with patients without MS, regardless of the history of cardiovascular events [2].

Based on the monitoring of individuals after genetic testing and a critical analsis of the results of a prospective genetic analysis, information about the possibilities of pre-symptomatic (prognostic) genetic testing becomes more and more practical.

Candidate genes that determine susceptibility to the development of metabolic syndrome complications

Cardiovascular diseases (CVD) are one of the most important medical and social problems in the world and occupy one of the main places in the structure of total mortality [1]. Among them, acute cerebrovascular accidents (stroke) and coronary (ischemic) heart disease (IHD) most often lead to the death of the patient. In addition, in recent years, the prevalence of these diseases has increased, especially among the able-bodied population, which often leads to persistent impairment of life and disability of patients. Therefore, along with the treatment of diseases, preventerology (disease prevention) is becoming increasingly important, including using modern molecular genetic research methods.

According to the publications, among the candidate genes that can determine the susceptibility to the development of complications of the metabolic syndrome can be divided into several groups: genes of the blood pressure regulation system, genes of the hemostasis system, and genes of the inflammatory process regulation system.

Blood pressure regulation system

The development of hypertension is predicted taking into account the possible increase in the tone of resistive vessels due

to increased formation of angiotensin II, due to a genetically determined increase in the synthesis of angiotensinogen. AGT gene encodes an angiotensinogen protein - serum globulin of the alpha globulin fraction, produced mainly by the liver cells, from which angiotensin I is produced by renin. The gene is on chromosome 1 (1q42.2) [3].

The AGT gene encodes the synthesis of angiotensinogen, which is a serum protein of the α-globulin fraction, with a molecular weight of about 65 kDa. AGT is synthesized mainly by the liver, adipocytes of adipose tissue; its synthesis is controlled by estrogens, glucocorticoids, and thyroid hormones. The proteolytic enzyme renin contributes to the transformation of AGT into inactive angiotensin-I. Under the action of an angiotensin converting enzyme and a number of alternative pathways involving chymases, cathepsin G, tonin and other serine proteases, angiotensin-I is converted into the biologically active substance angiotensin-II, which realizes its effect through angiotensin receptors [4,5].

The most significant from a clinical point of view, the variants of the AGT gene are due to point nucleotide polymorphisms, leading to amino acid substitutions in the 174 and 235 codons of the gene -T174M (rs4762) and M235T (rs699), respectively. They determine an increased level of angiotensinogen expression, which is regarded as a risk factor for the development of arterial hypertension. The incidence of unfavorable variants 174M and 235T in Caucasians is 10–15% and 15–20%, respectively.

Hemostasis system

Fibrinogen (factor I) is one of the main factors of the coagulation system, which is involved in the process of hemostasis. In addition to its role in the coagulation reaction, fibrinogen is involved in the pathogenesis of atherosclerosis, promoting adhesion of platelets and leukocytes to the surface of the endothelium and modulation of plasmin binding to its receptor. Data from epidemiological studies and meta analyzes show that elevated plasma levels of fibrinogen are associated with an increased risk of coronary artery disease and myocardial infarction (myocardial infarction). An increase in plasma fibrinogen by 1 g/l is associated with a more than twofold increase in the risk of coronary artery disease, stroke and cardiovascular mortality [6]. High plasma concentration of fibrinogen is considered an independent predictor of the risk of myocardial infarction [7].

The FGB gene encoding the β-chain of fibrinogen can certainly be considered as one of the important candidate genes, since fibrinogen serves as a substrate for thrombin, and as a result of its proteolytic cleavage, a fibrin clot is formed. Fibrinogen plays an important role in the process of platelet aggregation, that is, it is one of the main factors affecting the blood plasma viscosity. In the promoter region of the FGB gene in position –455, single nucleotide polymorphism G / A was found.

The prevalence of such polymorphism is from 5 to 10% in the general population. The polymorphic marker G (–455) A of the FGB gene is associated with the level of fibrinogen in the blood plasma. It is known that the presence of the -455A allele leads to an increase in gene expression by 1.2–1.5 times, as a result, to an increased level of fibrinogen in the blood by 10–30% and an increased risk of developing IHD, acute coronary syndrome, peripheral artery disease and stroke in adults [8,9].

In vitro studies have shown that the FGB –455A allele, associated with an elevated level of fibrinogen, impairs binding to the repressor protein, as a result of which FGB chain transcription increases [10].

Regulation of inflammation

In a fundamental and clinical study, evidence was obtained that inflammatory mechanisms play a central role in the pathogenesis and progression of atherosclerosis, plaque separation, thrombosis, and stroke. IL-6 has been shown to affect the synthesis of proteins of the acute phase of inflammation by hepatocytes and contributes to an increase in the concentration of C-reactive protein (CRP), one of the markers for the development of inflammation and acute myocardial infarction [11]. It should be noted that the peak concentration of CRP correlates with the maximum increase in the concentration of IL-6 [12]. Elevated levels of IL-6 are associated with the development [13] and severity of coronary disease [14], with the development of processes in the atherosclerotic plaque and the subsequent acute coronary event [15]. There are opinions that, despite the fact that such processes are characterized by the activity of acute-phase proteins, an increase in the concentration of IL-6 may be an additional marker for the development of the pathological process in the vascular bed [16].

A number of studies have identified significant imbalances between pro-inflammatory (TNFα, IL-6, IL-8) and anti-inflammatory cytokines (IL-4) in patients with IHD and dyslipidemia (elevated cholesterol (CH) and low-density lipoproteins (LDL)). A linear relationship was found between the serum IL-6 level and the level of very low-density lipids (VLDL) [17]. IL-6 is believed to affect adipose tissue function and plasma lipid levels [18]. According to some data, up to 30% of serum IL-6 is secreted by adipose tissue, which cannot be ignored, since overweight is one of the risk factors for cardiovascular disease and the development of an acute coronary event - possibly due to the activation and intensification of the inflammatory process [19,20]. The relationship between the increase in systolic pulse and mean blood pressure with the level of IL-6. Individual differences in the plasma level of IL-6 among Caucasoids are shown, and screening studies revealed that the level of IL-6 was higher in those who subsequently suffered a myocardial infarction [21].

The C174G polymorphism in the promoter region of the IL-6 gene affects gene transcription and, accordingly, the expression of this cytokine, which ultimately controls sereum level of interleukin-6 [22].

Materials and Research Methods

Examined group consisted of 135 patients who were divided into 2 subgroups: 1 subgroup (101 patients) with acute cerebral circulation

impairment, 2 sub-groups (34 patients (No. of patients 69-102)) with hypertension, obesity, type 2 diabetes mellitus. Selection of groups was carried out taking into account the preclinical stage of the disease. Mean age in group 1 among women M ± SD = 66.6 ± 12,4; men - M ± SD = 62.88 ± 11,6 at P<0.05; in the second group, respectively M ± SD = 46, 87 ± 12,0; men - M ± SD = 42.09 ± 8,9 at P<0.05. QR = respectively in group 1-67.0 (58.0 ÷ 77.0), QR men – 65.0 (55.0 ÷ 71.0); in the second group, respectively 44.0 (36.0 ÷ 59.0) and men – 39.0 (35.0 ÷ 47.0).

DNA isolation was performed for subsequent genotyping from whole blood with S-Sorb reagent kits from Syntol using silica sorbent. To study the genetic susceptibility to complications of metabolic syndrome, a complex of genetic polymorphisms has been selected. Genotyping has been performed for the fol-lowing genes:

- Blood pressure regulation system –Thr174Met (rs4762) polymorphism of angiotensin gene (AGT), G83A (rs2368564) polymorphism of renin gene (REN);
- Sympathoadrenal system – Arg16Gly (rs1042713) polymorphism of beta-2 adrenergic receptor gene (ADRB2);
- Coagulation system –G-455A (rs1800790) polymorphism of fibrinogen gene (FGB);
- Regulation of inflammation – C174G (rs1800795) polymorphism of interleu-kin-6 gene (IL6);
- Nitric oxide biosynthesis system –Glu298Asp (rs1799983) polymorphism of endothelial NO synthase gene (eNOS);
- Homocysteine and folate metabolism system – C677T (rs1801133) polymorphism of methylenetetrahydrofolate reductase gene (MTHFR).

Single nucleotide polymorphisms (SNPs) of the studied genes were detected using the "real-time" polymerase chain reaction method with Syntol reagent kits with specific oligonucleotide primers and TaqMan probes.

Statistical processing was carried out using the STATISTICA 10.0 software (Stat Soft Inc., USA). Analysis of differences between groups in the distribution of genotypes and alleles was carried out using the contingency table and calculating the chi-square test.

If the expected frequencies were less than 10, the chi-square test with Yates correction was applied. Analysis of the compliance of the distribution of genotypes of the examined patients with the Hardy-Weinberg law was carried out by the chi-square test. The relationship between risk factor and outcome was estimated by the odds ratio (OR) calculated with a 95% confidence interval (CI). The significance level was considered statistically significant: p <0.05. The p values 0<0.05 in the range of 0.051-0.099 were regarded as statistically significant at the trend level.

Result and Discussion

The results of the genotyping of mononucleotide genetic polymorphisms in all the examined individuals are presented in Table 1.

No	FGB G455A rs1800790	AGT Thr174 Met rs4762	IL6 C174G rs1800795	REN G83A rs2368564	eNOS Glu-298Asp rs1799983	MTHFR C677T rs1801133	ADRB2 Arg16Gly rs1042713
1	GA	CC	GG	AA	GT	CT	AG
2	GG	CC	CC	GA	TT	CC	GG
3	GG	CC	GG	AA	GG	CC	GG
4	GA	CC	CG	GA	GG	CT	AA
5	GG	CC	GG	AA	GT	CC	AG
6	GA	CC	CG	GG	GG	CT	GG
7	GG	CC	CG	GG	GG	CT	GG
8	GG	CT	GG	GA	GT	CT	GG
9	GG	CT	CG	GG	GT	TT	AG
10	GA	CT	CG	GG	GT	CC	AG
11	GG	CC	CG	AA	GT	CC	AG
12	GG	CT	GG	GG	GT	CT	AG
13	GA	CC	CG	GA	GG	CC	AG
14	GG	CC	GG	GA	GT	CT	GG
15	GG	CC	CG	GA	GT	CC	AG
16	GA	CC	CG	GA	GT	CT	AG
17	GA	CC	CG	GA	GT	CC	AA
18	GG	CC	CC	GG	GG	TT	AG
19	GA	CC	CG	GA	GG	CT	GG
20	GA	CC	CG	AA	GT	CC	AA
21	GA	CC	CC	GG	GT	TT	AA
22	GG	CT	CG	GA	GG	CC	AG
23	GA	CC	CG	GG	GG	TT	GG
24	GG	CC	CG	GG	GG	CT	AG
25	GG	CT	CG	GA	GG	CT	GG
26	GA	CC	GG	GA	GT	CC	GG
27	GG	CC	CC	GA	GG	CC	GG
28	GG	CC	GG	GA	GT	CC	AA
29	GG	CC	CG	GG	GG	CT	AG
30	GG	CC	GG	GG	GT	CT	GG
31	GG	CT	CG	GG	GG	CT	AG
32	GG	CC	GG	GG	GG	CT	AG
33	AA	CC	CG	GA	TT	CC	AG
34	GA	CC	CC	GG	GG	CT	AG
35	GA	CT	CG	AA	GG	CT	AG
36	AA	TT	CC	GA	GT	CC	AG
37	AA	CT	CC	GG	GG	CT	AG
38	GG	CC	CC	GA	GG	CT	AG
39	GA	CC	GG	GA	GT	CT	AG
40	GG	CC	CC	GG	GG	TT	AG
41	GG	CT	CG	GG	GG	CT	AG
42	GG	CC	GG	GG	GT	CT	GG
43	GA	CC	GG	GG	GG	CC	AG
44	GA	CC	GG	GG	TT	CT	AG
45	GA	CC	CG	GG	GT	CT	AG
46	GG	CC	GG	GA	GG	TT	AG
47	GA	CC	CG	GG	GT	CC	AG

48	GG	CC	CC	GG	GG	CC	AA
49	GG	CT	GG	GA	GG	CT	AA
50	GG	CT	GG	GG	GT	CC	AG
51	AA	CC	GG	GG	GG	CC	AG
52	GG	CC	CG	GA	GG	CT	AG
53	GA	CC	GG	GA	GG	TT	GG
54	GA	CC	CG	GA	GG	CT	GG
55	GA	CC	CG	AA	GT	CC	AA
56	GG	CC	GG	GG	GG	CC	AA
57	GG	CC	CG	AA	GT	CC	AG
58	GA	CC	CG	AA	GG	CT	AG
59	GA	CC	CG	GA	GG	CC	GG
60	GA	CC	CG	GA	GT	CC	AG
61	AA	CC	CG	AA	GG	CT	AG
62	GA	CC	GG	GG	GT	CT	GG
63	GG	CC	CG	AA	GT	CC	AG
64	GA	CC	CG	GG	GT	CC	GG
65	GA	CC	CC	GG	GG	CC	AG
66	GA	CC	GG	GA	GG	CT	AG
67	GA	CT	CC	GA	GG	CT	GG
68	GG	CT	CG	GG	TT	CT	GG
69	GA	CC	CG	GA	GT	CT	AG
70	GG	CC	CG	GA	GT	CT	GG
71	GA	CC	CG	GG	GG	CT	AG
72	GG	CC	CG	GA	GG	CC	AA
73	GA	CC	CC	GG	GG	CC	AG
74	GA	CT	GG	GA	GG	TT	GG
75	GG	CC	CG	GA	GT	CC	AA
76	GG	CT	CC	GG	GT	CT	GG
77	GA	CC	CC	GG	GT	CC	GG
78	GA	CC	CC	GG	GG	CC	AA
79	GG	CC	CG	GA	GG	TT	AA
80	GA	CC	CC	AA	GT	CT	AG
81	GG	CT	GG	GG	GT	CT	AG
82	GG	CT	GG	GG	GT	CC	AA
83	AA	CC	CC	GG	GG	CT	AG
84	GA	CT	GG	GA	GT	CC	AA
85	GG	CT	GG	GA	GG	CC	AG
86	GA	CC	CC	GA	TT	CC	GG
87	GA	CC	CG	GG	GG	CC	AG
88	GA	CC	CG	GG	GT	CC	AG
89	GG	CC	GG	GG	GG	CT	GG
90	GG	CT	CC	GA	GT	CT	AG
91	GG	CT	CG	AA	GG	CC	GG
92	GA	CT	CG	GA	GG	CC	GG
93	GG	CT	CC	GG	GG	CC	AA
94	GG	CT	CG	GG	GG	CC	GG
95	GG	CC	GG	GG	GT	TT	GG
96	GG	CC	CG	GG	TT	CC	AG
97	GG	CC	CG	AA	GT	CC	AG
98	GG	CC	CG	GG	GT	CT	GG
99	GG	CC	CC	GA	GG	CC	GG
100	GG	CC	CG	GA	GT	CT	AG
101	GG	CT	GG	GA	GT	CT	AG
102	AA	CC	GG	GG	GG	CT	GG
103	GG	CC	CG	AA	GG	TT	AA
104	GG	CT	CC	GG	GT	TT	GG
105	GA	CC	GG	GA	GG	CC	AG
106	GA	TT	CG	GG	GG	CT	AG
107	GG	CT	GG	GA	TT	CC	GG
108	AA	TT	CG	GG	TT	CT	GG
109	GA	CC	CG	GA	TT	CT	AA
110	GA	CC	CG	GA	GT	CT	AA
111	GG	CC	CG	GA	GT	CT	AG
112	GA	CT	CG	AA	GT	CT	AG
113	GA	CC	GG	GG	GG	CT	AA
114	GG	CT	CG	GA	GT	CT	AA
115	AA	CC	CG	GA	GT	CC	AA
116	GG	CC	CG	GG	GG	CT	AG
117	GG	CC	CG	GG	GG	CT	AG
118	GA	CT	CG	GG	GG	CC	GG
119	GA	CC	CC	GG	GT	CC	GG
120	GG	CC	GG	GA	GG	CC	AG
121	GA	CC	CC	GG	GG	CC	AG
122	GA	CT	GG	GG	GT	CT	AG
123	GA	CC	CC	GG	GT	CC	GG
124	GG	CC	GG	GG	GG	CT	AA
125	GG	CC	GG	GA	GG	CC	GG
126	GA	CC	CG	GG	GG	CT	GG
127	GG	TT	CC	GG	GT	CT	GG
128	GG	CT	CC	GG	GG	CT	AG
129	GG	CT	GG	GA	GT	CT	AG
130	GA	CT	GG	GG	GG	CC	AG
131	GG	CC	CG	GA	GG	CT	AA
132	GA	CT	CG	GG	GT	CT	AG
133	GA	CC	GG	GG	GG	CC	GG
134	GG	CT	CC	GA	GT	CC	GG
135	GG	CC	CG	GG	GG	CC	AG

Table 1: Results of genotyping of single nucleotide genetic polymorphisms in the examined individuals.

An individual analysis of the combination of single nucleotide polymorphisms among the examined individuals showed that at least one homozygous variant for the risk allele among the genes studied was found in 39.3% of persons, two homozygous variants - 13.3% and three - 3.7%.

It was shown that the frequency distribution of genotypes of the studied genes in the examined individuals corresponds to the Hardy-Weinberg law (χ^2 <2.71 with df = 1). The results of genetic

studies were compared to the prevalence of gene polymorphisms in the European population according to the 1000 Genome Project, a joint international initiative to create the most detailed card of human genetic variations for today, including single-nucleotide polymorphisms, structural variants and haplotype context (The Ensembl Project, http: /www.ensembl.org/), this data was used as a population control. The distribution of genotypes and alleles by the studied loci and data on the assessment of the statistical significance of the differences between groups and subgroups are presented in table 2.

Distribution of genotypes of the assessed genes in different groups (table 2), it is shown that the AG genotype of the FGB gene (G455A) is found more often in 1 subgroup (individuals with stroke) in 29.6% compared to the European population - in 29, 2% ($p < 0.01$). Thus, the carriage of the AG genotype of the FGB gene (G455A), associated with an increased level of plasma fibrinogen and resulting hypercoagulability, is associated with an increased risk of developing stroke (OR = 1,946, 95% CI = 1,257-3.012). Differences in frequency of the TT genotype of the eNOS gene (Glu298Asp) in the examined patients as compared

SNP	Genotype/ allele	All examined		Subgroup 1		Subgroup 2		Population control		Significance of differences between groups			
		1		2		3		4		P1-4	P2-4	P3-4	P2-3
		N	%	N	%	N	%	N	%				
FGB G455A rs1800790	GG	69	51.1	49.0	48.5	20.0	58.8	321.0	63.8	0.0072	0.0040	0.5583	0.2983
	AG	57	42.2	45.0	44.6	12.0	35.3	147.	29.2	0,0040	0,0025	0,4531	0,3444
	AA	9	6.7	7.0	6.9	2.0	5.9	35.0	7.0	0,9055	0,9921	0,8106	0,8321
	G	72.2%		70.8%		76.5%		78.4%		0,0311	0,0183	0,7045	0,3659
	A	27.8%		29.2%		23.5%		21.6%					
AGT Thr174Met rs4762	CC	94	69.6	72.0	71.3	22.0	64.7	381.0	75.7	0,1480	0,3450	0,1500	0,4704
	CT	37.0	27.4	25.0	24.8	12.0	35.3	113.0	22.5	0,2292	0,6173	0,0867	0,2333
	TT	4.0	3.0	4.0	3.9	0.0	0.0	9.0	1.8	0,3914	0,1700	0,4315	0,2388
	C	83.3%		83.7%		82.4%		87.0%		0,1213	0,2094	0,2773	0,8020
	T	16.7%		16.3%		17.6%		13.0%					
IL6 C174G rs1800795	GG	41.0	30.4	32.0	31.7	9.0	26.5	181.0	36.0	0,2240	0,4091	0,2615	0,5675
	CG	65.0	48.1	50.0	49.5	15.0	44.1	226.0	44.9	0,5051	0,3997	0,9265	0,5866
	CC	29.0	21.5	19.	18.8	10.0	29.4	96.0	19.1	0,5334	0,9490	0,1432	0,1930
	G	54.4%		56.4%		48.5%		58.4%		0,2371	0,5966	0,1089	0,2575
	C	45.6%		43.6%		51.5%		41.6%					
REN G83A rs2368564	CG	66.0	48.9	49.0	48.5	17.0	50.0	281.0	55.9	0,1485	0,1757	0,5054	0,8809
	GA	53.0	39.2	39.0	38.6	14.	41.2	183.0	36.4	0,5386	0,6711	0,5745	0,7913
	AA	16.0	11.9	13.0	12.9	3.0	8.8	39.0	7.8	0,1320	0,0943	0,8221	0,5276
	G	68.5%		67.8%		70.6%		74.1%		0,0692	0,0685	0,5290	0,6709
	A	31.5%		32.2%		29.4%		25.9%					
eNOS Glu298Asp rs1799983	GG	69.0	51.1	53.0	52.5	16.0	47.0	223.0	44.3	0,1605	0,1339	0,7570	0,5847
	GT	57.0	42.2	41.0	40.6	16.0	47.0	214.0	42.5	0,9463	0,7172	0,6067	0,5092
	TT	9.0	6.7	7.0	6.9	2.0	6.0	66.0	13.1	0,0387	0,0816	0,2193	0,8321
	G	72.2%		72.8%		70.6%		65.6%		0,0401	0,0484	0,4016	0,7280
	T	27.8%		27.2%		29.4%		34.4%					
MTHFR C677T rs1801133	CC	59.0	40.6	43.7	40.6	18.0	52.9	204.0	40.6	0,5095	0,2287	0,1558	0,2093
	CT	64.0	47.4	51.0	50.5	13.0	38.3	231.0	45.9	0,7590	0,4008	0,3835	0,2156
	TT	12.0	8.9	9.0	8.9	3.0	8.8	68.0	13.5	0,1492	0,2051	0,4341	0,9876
	C	67.4%		65.8%		55.1%		63.5%		0,2362	0,5305	0,1555	0,3441
	T	32.6%		43.2%		44.9%		36.5%					
ADRB2 Arg16Gly rs1042713	GG	44.0	32.6	31.0	30.7	13.0	38.2	183.0	36.4	0,4142	0,2754	0,8280	0,4171
	AG	67.0	49.6	53.0	52.5	14.0	41.2	252.0	50.1	0,9228	0,6630	0,3139	0,2544
	AA	24.0	17.8	17.0	16.8	7.0	20.6	68.0	13.5	0,2110	0,3823	0,2498	0,6202
	G	57.4%		56.9%		58.8%		61.4%		0,2296	0,2321	0,6692	0,7848
	A	42.6%		43.1%		41.2%		38.6%					

Table 2: The distribution of genotypes and alleles for the studied loci in the compared groups.

with the population control were also revealed, which may be due to the distribution of this variant of the gene among the Russian population. At the level of the statistical trend (0.051 <p <0.099), differences were found in the frequency of allele A of the REN gene (G83A) associated with an elevated level of renin, which was detected in 32.2% in individuals of subgroup 1, 25.9% in the European population. No significant differences were found in the frequency of genotypes and alleles when compared with subgroup 2, which may be due to the small number of examined groups.

Conclusion

Known pathogenic mechanisms of the metabolic syndrome and its complications and previously performed domestic and foreign studies on the role of genetic polymorphisms in the development of this pathology allowed us to determine the key systems for the development of fatal complications of the metabolic syndrome: blood pressure regulation system, sympathoadrenal system, coagulation system, regulation of inflammation, nitric oxide biosynthesis system, folate and homocysteine metabolism system.

Based on the analysis of results obtained, we can identify the most informative markers for assessing the risk of the possibility of the development of fatal complications of the metabolic syndrome: G-455A (rs1800790) polymorphism of the fibrinogen gene (FGB), Glu298Asp (rs1799983) polymorphism of endothelial NO synthase gene (eNOS), G83A rs2368564) polymorphism of renin gene (REN).

To assess the risk of developing and predict the course of multifactorial pathology, the most informative is the assessment of a complex of single nucleotide polymorphisms of genes of various systems, which is determined by the presence of a synergistic interaction of genetic polymorphisms, when the presence of unfavorable variants of genes of several systems increases the probability of developing the disease and its more severe course.

An individual approach to the patient, based on an adequate interpretation of the results of genetic research and their comparison with the data of clinical, laboratory and instrumental tests, will allow early diagnosis of genetically determined diseases and offer the most effective scheme of preventive and therapeutic measures. To develop a methodology for assessing the risk of fatal complications of the metabolic syndrome among the working-age population of Veliky Novgorod, it is necessary to continue research on a larger sample and assess the prevalence of the studied gene variants among practically healthy individuals in the same region, matched by gender and age with the main group.

Thus, it is proved that the genetic risk of the main components of the metabolic syndrome are the following genes:

Genetic risk of hypertension

- Angiotensinogen (AGT). Detection of mutation C521T (Thr174Met)
- Aldosterone synthase (CYP11B2). The identification of mutations of C (-344)T (a regulatory region of a gene)
- Guanine is a beta-3 nucleotide binding protein (GNB3). The identification of mutations C825T (Ser275Ser)
- Adducin 1 (alpha) (ADD1). The identification of mutations G1378T (Gly460Trp)
- Angiotensin II receptor type II (AGTR2). The identification of mutations G1675A
- Endothelial nitric oxide synthase (NOS3). Detection of mutation G894T (Glu298Asp)
- Endothelial nitric oxide synthase (NOS3). The identification of mutations of T(-786)C
- Angiotensinogen (AGT). The identification of mutations T704C (of met235thr)
- Angiotensin receptor 1 (AGTR1). Detection of mutation A1166C (regulatory region of the gene)
- Angiotensin converting enzyme (ACE). Detection of Alu Ins/Del mutation

Genetic risk of hyperglycemia and obesity

- Melatonin receptor 1B (MTNR1B). Detection of mutation C(g.37979623)T - Marker is associated with changes in glucose metabolism. It is investigated to identify genetic predisposition to increased blood glucose level, type 2 diabetes.
- Beta-2-adrenergic receptor (ADRB2). Detection of mutation G46A (Arg16Gly) Genetic marker is associated with the peculiarities of neural receptors. It is studied to identify predisposition to metabolic syndrome, obesity, bronchial asthma, including its nocturnal form, the risk of hypertension in patients with type 2 diabetes mellitus. It is important in assessing the effectiveness of treatment of asthma.
- Beta-3 adrenergic receptor (ADRB3). The identification of mutations T190C (Trp64Arg). B3-adrenergic receptor (β3-AR, ADRB3) is an important component of the sympathetic nervous system, which primarily mediates lipolysis (destruction of fat cells, adipocytes) and thermoregulation. Adrb3 GENE dysfunction is typical for the development of diseases such as hypertension, diabetes, obesity, etc.
- Apolipoprotein E (ApoE). The marker is associated with changes in lipoprotein metabolism. Investigated for the detection of genetic predisposition to myocardial infarction, giperholesterinemia, Alzheimer's disease, memory disorders in elderly, rasseyannogo sclerosis, dementia. It has prognostic significance in traumatic brain injuries.
- Receptor activated by peroxisome proliferators, gamma (PPARG). The identification of mutations C68777G (Pro12Ala) the Marker is associated with the peculiarities of piroxicam. It is investigated to identify the effectiveness of aerobic training and insulin resistance in type 2 diabetes, predisposition to weight gain, accumulation of adipose tissue, type 2 diabetes, the development of edema in patients with type 2 diabetes.
- Coactivator 1 of the alpha receptor activated by peroxisome proliferators, gamma (PPARGC1A). The identification of mutations G1444A (Gly482Ser) the Marker is associated with the peculiarities of piroxicam. It is investigated to identify the type of muscle activity and fat burning efficiency.

- Gene associated with fat mass and obesity (FTO). The identification of mutations G(45+52261)A (a regulatory region of a gene). The marker is associated with the activity of accumulation of adipose tissue. It is investigated to identify the genetic predisposition to increase body weight.

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