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RELATIONSHIP OF THE GESTATIONAL AGE OF A PREMATURE NEWBORN WITH A HEREDITARY PREDISPOSITION TO METABOLIC SYNDROME

Part II. Associations of molecular genetic predictors of overweight and type 2 diabetes mellitus with the gestational age of premature newborns

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Abstract. The aim of the study was to evaluate the frequency of carrier allelic variants of polymorphic loci of genes predisposing to overweight and type 2 diabetes mellitus, depending on the gestation period of a premature newborn. The study design is prospective, controlled, single — center, non-randomized. Genomic DNA samples were studied in newborns with extremely low body weight (ELBW) and gestational age ≤28 weeks (n=95), premature newborns (PN) with gestational age >28 and ≤34 weeks (n=105), as well as a population sample of adults (n=100). For the analysis, we selected loci with a well — known association with the development of overweight and type 2 diabetes — *ADRB2* (rs1042713) and (rs1042714), *ADRB3* (rs4994), *GNB3* (rs5443), *PPARA* (rs4253778), *PPARD* (rs2016520), *TCF7L2_IVS3* (rs7903146) and *TCF7L2_IVS4* (rs12255372), *PPARGC1A* (rs8192678), *MTHFR* (rs1801131), *PPARG* (rs1801282), *MTNR1B* (rs10830963), *SIRT1* (rs7069102). The distribution of allele frequencies between the study groups was compared. PN are significantly more likely to be carriers of the A allele and the AA genotype of the rs8192678 locus in the *PPARGC1A* gene. In newborns with ELBW, we additionally revealed a more frequent occurrence of the C allele and the CC genotype of the rs4253778 locus in the *PPARA* gene. It is established newborns with ELBW are more frequent carriers of rare allelic variants of genes predisposing to metabolic syndrome

Key words: *premature newborns, metabolic syndrome, hereditary predisposition, gene polymorphism*

ВЗАИМОСВЯЗЬ ГЕСТАЦИОННОГО ВОЗРАСТА НЕДОНОШЕННОГО НОВОРОЖДЕННОГО С НАСЛЕДСТВЕННОЙ ПРЕДРАСПОЛОЖЕННОСТЬЮ К МЕТАБОЛИЧЕСКОМУ СИНДРОМУ

Часть II. Ассоциации молекулярно-генетических предикторов избыточной массы тела и сахарного диабета 2-го типа с гестационным возрастом недоношенных новорожденных

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Резюме. Цель работы — оценка частоты носительства аллельных вариантов полиморфных локусов генов предрасположенности к ожирению и сахарному диабету 2-го типа в зависимости от срока гестации недоношенного новорожденного. Дизайн исследования: проспективное, контролируемое, одноцентровое, нерандомизированное. Изучались образцы ДНК у новорожденных с экстремально низкой массой тела (ЭНМТ) и гестационным возрастом ≤28 недель (n=95), недоношенных новорожденных (НН) с гестационным возрастом >28 и ≤34 недель (n=105), и популяционной выборки взрослых (n=100). Для анализа были выбраны локусы с уже известной ассоциацией к развитию ожирения и сахарного диабета 2-го типа — *ADRB2* (rs1042713) и (rs1042714), *ADRB3* (rs4994), *GNB3* (rs5443), *PPARA* (rs4253778), *PPARD* (rs2016520), *TCF7L2*_IVS3 (rs7903146) и *TCF7L2*_IVS4 (rs12255372), *PPARGC1A* (rs8192678), *MTHFR* (rs1801131), *PPARG* (rs1801282), *MTNR1B* (rs10830963), *SIRT1* (rs7069102). Проводилось сравнение распределения частот аллелей между исследуемыми группами пациентов. НН достоверно чаще являются носителями аллеля A и генотипа AA локуса rs8192678 гена *PPARGC1A*. У новорожденных с ЭНМТ дополнительно выявлена более частая встречаемость аллели C и генотипа CC локуса rs4253778 гена *PPARA*. Установлено, что новорожденные с ЭНМТ являются более частыми носителями редких аллельных вариантов генов предрасположенности к метаболическому синдрому.

Ключевые слова: *недоношенные новорожденные, метаболический синдром, наследственная предрасположенность, полиморфизм генов*

INTRODUCTION

Incidence of preterm birth has increased significantly over the past 50 years and now affects nearly 11% of all newborns [1]. During the same period, medical advances have led to a significant improvement in the survival rate. Currently, more than 95% of premature neonates receiving modern neonatal and pediatric care survive to adulthood [2, 3]. Consequently, an unprecedented number of preterm birth survivors are now transitioning to adulthood each year (>10 million per year worldwide) [4]. This trend will have growing clinical importance. Therefore, clinicians who provide adult health care will increasingly encounter patients having undergone preterm birth. From this perspective, particularly, mechanisms and predictors of metabolic syndrome (MS), with obesity, arterial hypertension, and type 2 diabetes mellitus as its main manifestations, are being actively studied [5].

The genetic basis of MS predisposition has been poorly examined so far. There is evidence that predisposition to the disease may have hereditary nature. Although the clinical relevance of presumed genetic markers still requires convincing confirmation [6–8].

AIM

The aim of the research was to evaluate the frequency of carrying allelic variants of genes predisposing to overweight and type 2 diabetes mellitus in preterm newborns depending on gestational age.

MATERIALS AND METHODS

Research design: prospective, controlled, single-center, non-randomized. The research was performed on the base of the Republican Clinical Perinatal Center of the Republic of Bashkortostan in the period from 01.02.2019 to 01.03.2020. The research was approved by the ethical committee of the State Budgetary Institution "Republican Children's Clinical Hospital" of the Ministry of Health of the Republic of Bashkortostan (Protocol No. 9 of 21.01.2019).

Table 1. Demographic characteristics of the studied groups of children

Таблица 1. Демографические характеристики исследуемых групп детей

Показатель / Indicator	Экстремально низкая масса тела / Extremely low body weight (n=95)	Недоношенные новорожденные / Premature newborns (n=105)
Вес, г	874,7±181,86	1486,54±482,31
Рост, см	33,55±3,33	43,32±5,14
Гестационный возраст, недели	26,79±1,39	32,23±2,39

Genomic DNA samples were collected from neonates with extremely low birth weight (ELBW) below 1000 g and gestational age of 28 weeks or less (ELBW group; n=95); premature neonates (PN) with low birth weight less than 2000 g but more than 1000 g and gestational age less than 34 weeks but more than 28 weeks (PN group; n=105), as well as a population sample of adults from the Republic of Bashkortostan (control, n=100) (Table 1).

Molecular genetic tests were performed at the Center of Molecular Medicine of Bashkir State University, Ufa. DNA samples (repeats) isolated from peripheral blood lymphocytes of the examined neonates served as a material for the tests. The quality and quantity of isolated genomic DNA were examined using a Qubit 3.0 fluorimeter (Invitrogen, USA). Amplification was performed using reagent kits from Syntol, Russia, on a CFX96 Touch Real Time System detection amplifier (BioRad, USA). All loci were genotyped by real-time polymerase chain reaction (PCR) in the presence of fluorescent probes using Taqman technology according to the manufacturer's protocol (Syntol LLC, Russia).

The loci which are associated with development of MS (overweight, hyperglycemia) were selected for analysis: the beta-2-adrenergic receptor gene — *ADRB2* (rs1042713) and *ADRB2* (rs1042714), the beta-3-adrenergic receptor gene — *ADRB3* (rs4994), guanine nucleotide-binding protein beta-3 — *GNB3* (rs5443), peroxisome proliferator-activated receptor gene — *PPARA* (rs4253778), peroxisome proliferator-activated receptor protein delta gene — *PPARD* (rs2016520), T-cell transcription factor 4 gene — *TCF7L2_IVS3* (rs7903146) and *TCF7L2_IVS4* (rs12255372), peroxisome proliferator-activated receptor gamma coactivator 1-alpha gene — *PPARGC1A* (rs8192678), methylenetetrahydrofolate reductase gene — *MTHFR* (rs1801131), peroxisome proliferator-activated receptor gamma gene — *PPARG* (rs1801282), melatonin receptor 1B gene — *MTNR1B* (rs10830963), Sirtuin 1 gene — *SIRT1* (rs7069102).

Statistical analysis was performed according to the "case-control" type: where "case" is a sample of ELBW or PN, "control" is a population sample. The distribution of allele and genotype frequencies between the studied groups of individuals was compared.

Hardy–Weinberg equilibrium conditions were fulfilled for all polymorphic loci studied for both cases and controls. The χ^2 method was used to calculate associations. Inheritance was estimated using a multiplicative model. If there were statistically significant differences in the distribution of allele and genotype frequencies between the study groups, calculations for the dominant and recessive models were also performed.

RESULTS

The results of the analysis of allele and genotype frequency distribution of polymorphic loci of metabolic syndrome (MS) predisposition genes in the preterm neonates are presented in Table 2.

No statistically significant differences between groups ($p > 0.05$) in polymorphic loci distribution frequencies was shown for *ADRB2* (rs1042713, rs1042714).

In addition, no statistically significant differences between groups ($p > 0.05$) in polymorphic loci distribution frequencies was shown for genes polymorphic loci *ADRB3* (rs4994), *GNB3* (rs5443), *PPARA* (rs4253778), *PPARD* (rs2016520), *TCF7L2* (rs7903146) and *TCF7L2* (rs12255372), *MTHFR* (rs1801131), *MTNR1B* (rs10830963) and *SIRT1* (rs7069102).

No significant differences between the groups were also found in allele frequency distribution of the polymorphic locus *PPARG* (rs1801282). However, according to the dominant inheritance model, it was shown that the GG genotype was

Table 2. Comparative analysis of the distribution of allele frequencies of polymorphic loci of susceptibility genes to metabolic syndrome in the studied premature infants

Таблица 2. Сравнительный анализ распределения частот аллелей полиморфных локусов генов предрасположенности к метаболическому синдрому у исследуемых недоношенных детей

Аллели / Alleles	Случаи / Cases (n=105)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Аллель *A* rs1042713 в гене *ADRB2* / Allele *A* rs1042713 in the *ADRB2* gene	0.437	0.429	0.03	0.85	1.03	0.73–1.46
Аллель *G* rs1042713 в гене *ADRB2* / Allele *G* rs1042713 in the *ADRB2* gene	0.563	0.571			0.97	0.69–1.37
Аллель *C* rs1042714 в гене *ADRB2* / Allele *C* rs1042714 in the *ADRB2* gene	0.619	0.616	0.00	0.95	1.01	0.71–1.44
Аллель *G* rs1042714 в гене *ADRB2* / Allele *G* rs1042714 in the *ADRB2* gene	0.381	0.384			0.99	0.70–1.41
Аллель *T* rs4994 в гене *ADRB3* / Allele *T* rs4994 in the *ADRB3* gene	0.837	0.875	1.52	0.22	0.73	0.45–1.20
Аллель *C* rs4994 в гене *ADRB3* / Allele *C* rs4994 in the *ADRB3* gene	0.163	0.125			1.37	0.83–2.25
Аллель *T* rs5443 в гене *GNB3* / Allele *T* rs5443 in the *GNB3* gene	0.321	0.290	0.59	0.44	1.16	0.80–1.68
Аллель *C* rs5443 в гене *GNB3* / Allele *C* rs5443 in the *GNB3* gene	0.679	0.710			0.87	0.60–1.25
Аллель *G* rs4253778 в гене *PPARA* / Allele *G* rs4253778 in the *PPARA* gene	0.817	0.866	2.16	0.14	0.69	0.42–1.13
Аллель *C* rs4253778 в гене *PPARA* / Allele *C* rs4253778 in the *PPARA* gene	0.183	0.134			1.45	0.88–2.37
Аллель *A* rs2016520 в гене *PPARD* / Allele *A* rs2016520 in the *PPARD* gene	0.829	0.821	0.05	0.82	1.05	0.67–1.65
Аллель *G* rs2016520 в гене *PPARD* / Allele *G* rs2016520 in the *PPARD* gene	0.171	0.179			0.95	0.60–1.49
Аллель *C* rs7903146 в гене *TCF7L2* / Allele *C* rs7903146 in the *TCF7L2* gene	0.800	0.788	0.12	0.73	1.08	0.70–1.65
Аллель *T* rs7903146 в гене *TCF7L2* / Allele *T* rs7903146 in the *TCF7L2* gene	0.200	0.212			0.93	0.61–1.42
Аллель *G* rs12255372 в гене *TCF7L2* / Allele *G* rs12255372 in the *TCF7L2* gene	0.801	0.832	0.83	0.36	0.81	0.52–1.27
Аллель *T* rs12255372 в гене *TCF7L2* / Allele *T* rs12255372 in the *TCF7L2* gene	0.199	0.168			1.23	0.79–1.93
Аллель *G* rs8192678 в гене *PPARGC1A* / Allele *G* rs8192678 in the *PPARGC1A* gene	0.608	0.730	8.69	**0.003**	0.57	0.40–0.83
Аллель *A* rs8192678 в гене *PPARGC1A* / Allele *A* rs8192678 in the *PPARGC1A* gene	0.392	0.270			1.74	1.20–2.53
Аллель *A* rs1801131 в гене *MTHFR* / Allele *A* rs1801131 in the *MTHFR* gene	0.659	0.655	0.01	0.93	1.02	0.71–1.46
Аллель *C* rs1801131 в гене *MTHFR* / Allele *C* rs1801131 in the *MTHFR* gene	0.341	0.345			0.98	0.69–1.41
Аллель *C* rs1801282 в гене *PPARG* / Allele *C* rs1801282 in the *PPARG* gene	0.816	0.813	0.01	0.92	1.02	0.66–1.58
Аллель *G* rs1801282 в гене *PPARG* / Allele *G* rs1801282 in the *PPARG* gene	0.184	0.187			0.98	0.63–1.52

Ending of the table 2 / Окончание табл. 2

Аллели / Alleles	Случаи / Cases (n=105)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Аллель *C* rs10830963 в гене *MTNR1B* / Allele *C* rs10830963 in the *MTNR1B* gene	0.671	0.670	0.00	0.98	1.00	0.70–1.44
Аллель *G* rs10830963 в гене *MTNR1B* / Allele *G* rs10830963 in the *MTNR1B* gene	0.329	0.330			1.00	0.69–1.43
Аллель *C* rs7069102 в гене *SIRT1* / Allele *C* rs7069102 in the *SIRT1* gene	0.441	0.413	0.29	0.59	1.12	0.74–1.69
Аллель *G* rs7069102 в гене *SIRT1* / Allele G rs7069102 in the SIRT1 gene	0.559	0.587			0.89	0.59–1.35

Table 3. Comparative analysis of the distribution of allele frequencies of polymorphic loci of susceptibility genes to metabolic syndrome in studied newborns with extremely low body weight

Таблица 3. Сравнительный анализ распределения частот аллелей полиморфных локусов генов предрасположенности к метаболическому синдрому у исследуемых новорожденных с экстремально низкой массой тела

Аллели / Alleles	Случаи / Cases (n=95)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Аллель *A* rs1042713 в гене *ADRB2* / Allele *A* rs1042713 in the *ADRB2* gene	0.437	0.429	0.02	0.88	1.03	0.69–1.54
Аллель *G* rs1042713 в гене *ADRB2* / Allele *G* rs1042713 in the *ADRB2* gene	0.563	0.571			0.97	0.65–1.45
Аллель *C* rs1042714 в гене *ADRB2* / Allele *C* rs1042714 in the *ADRB2* gene	0.622	0.616	0.02	0.9	1.03	0.68–1.55
Аллель *G* rs1042714 в гене *ADRB2* / Allele *G* rs1042714 in the *ADRB2* gene	0.378	0.384			0.97	0.65–1.47
Аллель *T* rs4994 в гене *ADRB3* / Allele *T* rs4994 in the *ADRB3* gene	0.837	0.875	1.52	0.22	0.73	0.45–1.20
Аллель *C* rs4994 в гене *ADRB3* / Allele *C* rs4994 in the *ADRB3* gene	0.163	0.125			1.37	0.83–2.25
Аллель *T* rs5443 в гене *GNB3* / Allele *T* rs5443 in the *GNB3* gene	0.340	0.290	1.14	0.29	1.26	0.82–1.94
Аллель *C* rs5443 в гене *GNB3* / Allele *C* rs5443 in the *GNB3* gene	0.660	0.710			0.79	0.52–1.22
Аллель *G* rs4253778 в гене *PPARA* / Allele *G* rs4253778 in the *PPARA* gene	0.763	0.866	6.23	**0.01**	0.50	0.29–0.87
Аллель *C* rs4253778 в гене *PPARA* / Allele *C* rs4253778 in the *PPARA* gene	0.237	0.134			2.01	1.15–3.50
Аллель *A* rs2016520 в гене *PPARD* / Allele *A* rs2016520 in the *PPARD* gene	0.858	0.821	0.95	0.33	1.31	0.76–2.27
Аллель *G* rs2016520 в гене *PPARD* / Allele *G* rs2016520 in the *PPARD* gene	0.142	0.179			0.76	0.44–1.32
Аллель *C* rs7903146 в гене *TCF7L2* / Allele *C* rs7903146 in the *TCF7L2* gene	0.805	0.788	0.16	0.69	1.11	0.67–1.84
Аллель *T* rs7903146 в гене *TCF7L2* / Allele *T* rs7903146 in the *TCF7L2* gene	0.195	0.212			0.90	0.54–1.50
Аллель *G* rs12255372 в гене *TCF7L2* / Allele *G* rs12255372 in the *TCF7L2* gene	0.800	0.832	0.64	0.42	0.81	0.48–1.36
Аллель *T* rs12255372 в гене *TCF7L2* / Allele *T* rs12255372 in the *TCF7L2* gene	0.200	0.168			1.23	0.74–2.07

Ending of the table 3 / Окончание табл. 3

Аллели / Alleles	Случаи / Cases (n=95)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Аллель *G* rs8192678 в гене *PPARGC1A* / Allele *G* rs8192678 in the *PPARGC1A* gene	0.626	0.730	4.81	**0.03**	0.62	0.40–0.95
Аллель *A* rs8192678 в гене *PPARGC1A* / Allele *A* rs8192678 in the *PPARGC1A* gene	0.374	0.270			1.61	1.05–2.48
Аллель *A* rs1801131 в гене *MTHFR* / Allele *A* rs1801131 in the *MTHFR* gene	0.632	0.655	0.23	0.63	0.90	0.60–1.37
Аллель *C* rs1801131 в гене *MTHFR* / Allele *C* rs1801131 in the *MTHFR* gene	0.368	0.345			1.11	0.73–1.68
Аллель *C* rs1801282 в гене *PPARG* / Allele *C* rs1801282 in the *PPARG* gene	0.796	0.813	0.19	0.67	0.90	0.54–1.48
Аллель *G* rs1801282 в гене *PPARG* / Allele *G* rs1801282 in the *PPARG* gene	0.204	0.187			1.12	0.67–1.85
Аллель *C* rs10830963 в гене *MTNR1B* / Allele *C* rs10830963 in the *MTNR1B* gene	0.671	0.670	0.00	0.98	1.00	0.70–1.44
Аллель *G* rs10830963 в гене *MTNR1B* / Allele *G* rs10830963 in the *MTNR1B* gene	0.329	0.330			1.00	0.69–1.43
Аллель *C* rs7069102 в гене *SIRT1* / Allele *C* rs7069102 in the *SIRT1* gene	0.458	0.413	1.00	0.32	1.20	0.84–1.71
Аллель *G* rs7069102 в гене *SIRT1* / Allele *G* rs7069102 in the *SIRT1* gene	0.542	0.587			0.83	0.58–1.19

significantly less frequent among PN than in controls (0.5% vs 4.0%) — χ^2=4.92; p=0.03; OR 0.12; 95% CI 0.01–1.10.

At the same time, there were statistically significant differences in the distribution of allele frequencies (p=0.0003) of the polymorphic locus rs8192678 in the *PPARGC1A* gene between samples of preterm newborns and controls. The G allele and the GG genotype (according to the dominant inheritance model) appeared to be significantly less frequent among preterm infants (60.8% vs 73% and 43.2% vs 56.0%, respectively) — χ^2=8.69; p=0.003; OR 0.57; 95% CI 0.40–0.83 and χ^2=6.15; p=0.04; OR 0.60; 95% CI 0.37–0.97. Whereas the A allele and AA genotype, according to the recessive inheritance model, were significantly more frequent among preterm neonates than the population average, χ^2=8.69; p=0.003; RR 1.74; 95% CI 1.20–2.53 and χ^2=6.15; p=0.01; RR 2.48; 95% CI 1.19–5.18.

Analysis of allele frequency distribution of polymorphic loci of the above-mentioned genes among neonates with extremely low body weight are presented in Table 3.

No significant differences between groups (p >0.05) were found in the allele and genotype frequency distribution of polymorphic locus in genes *ADRB2* (rs1042714), *ADRB3* (rs4994), *PPARD* (rs2016520), *TCF7L2* (rs7903146), and *TCF7L2* (rs12255372), *MTHFR* (rs1801131), *PPARG* (rs1801282), *MTNR1B* (rs10830963) and *SIRT1* (rs7069102).

At the same time, there were found statistically significant differences in the distribution of allele frequencies (p=0.01) and genotype frequencies (0.03) of the polymorphic locus rs4253778 in the *PPARA* gene between the samples of neonates with ELBW and the comparison group. The G allele and the GG genotype (according to the dominant inheritance model) appeared to be significantly less frequent among ELBW than in controls (76.3% vs 86.6% and 55.1 vs 74.2%, respectively) — χ^2=6.23; p=0.01; OR 0.5; 95% CI 0.29–0.87 and χ^2=7.00; p=0.008; OR 0.43; 95% CI 0.23–0.81. The C allele was more frequently detected among ELBW, χ^2=6.23; p=0.01; OR 2.01; 95% CI 1.15–3.50.

There were revealed statistically significant differences in the allele frequency distribution (p=0.03) of the polymorphic locus rs8192678 in the *PPARGC1A* gene between the samples of ELBW and controls. The G allele was significantly less frequent among ELBW than in the control group (62.6% vs 73.0%) — χ^2=4.81; p=0.03; OR 0.62; 95%

CI 0.40–0.95. Whereas the A allele was significantly more frequently detected among ELBW than the population average (37.4% vs 27.0%) — χ^2=4.81; p=0.03; OR 1.61; 95% CI 1.05–2.48.

DISCUSSION

The study is devoted to the search for genetic risk factors of metabolic syndrome development which are associated with prematurity. Preterm infants are significantly more likely to carry allele A and homozygous genotype AA of the polymorphic locus in *PPARGC1A* (rs8192678). The gene is responsible for the production of protein coactivator 1-alpha-receptor, which is involved in the metabolism of muscle tissues, fats and carbohydrates [11].

Allele C and genotype CC of the polymorphic locus rs4253778 in the *PPARA* gene were also significantly more frequent in ELBW. PPARα receptor is one of the subtypes of cell nucleus receptors activated by Peroxisome Proliferator Activated Receptor (PPAR), which regulates lipid metabolism in the liver and skeletal muscles, as well as glucose homeostasis [9].

To some extent, the data obtained may indicate that premature newborns have some genetic predisposition to the development of metabolic syndrome. Moreover, this is more significant when the gestational age is less than 28 weeks. A number of independent studies conducted in recent years confirm our data [10–12].

The research has a few methodological limitations. These are, first of all, the relatively small number of patients, single-center design and lack of randomization. Another limitation is the fact that it was a single-stage study and not a longitudinal one. Therefore, the significance of the identified risk factors for metabolic syndrome remains relatively uncertain.

CONCLUSION

The research demonstrated that neonates with extremely low birth weight, in contrast to premature neonates with normal body weight, as a rule, carry a greater number of rare alleles of genes predisposing to metabolic syndrome, which may increase the risk of developing MS in adulthood.

The presented data allows us to assume that the impact of unfavorable environmental factors in development of MS may have a greater effect in neonates with ELBW. Moreover, individuals born earlier than 28 weeks of gestation are more predisposed to MS due to genetic risks, in addition to the factors described in the framework of the "fetal programming" theory.

ADDITIONAL INFORMATION

Author contribution. P.I. Mironov — concept and design of the study, processing of material, writing the article, literature analysis; Yu.S. Aleksandrovich — typing and processing of material, writing the article; O.H. Nurgalieva — typing and processing of material, writing the article; R.R. Valiev — performing genetic research, processing material, writing articles, analyzing literature; A.S. Bogdanova — performing genetic research; S.G. Petrova — performing genetic research; E.K. Khusnutdinova — reviewing intellectual content; D.O. Ivanov — reviewing intellectual content. All authors read and approved the final version before publication.

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