ISSN 2221-2582

UDC 616-06.391
DOI: 10.56871/CmN-W.2024.48.43.010

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

Part I. Associations of molecular genetic predictors of arterial hypertension with the gestational age of premature newborns

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For citation: Mironov PI, Ivanov DO, Aleksandrovich YuS, Nurgalieva AKh, Valiev RR, Bogdanova AA, Petrova SG, Khusnutdinova EK. Relationship of the gestational age of a premature newborn with a hereditary predisposition to metabolic syndrome. Part I. Associations of molecular genetic predictors of arterial hypertension with the gestational age of premature newborns. Children's Medicine of the North-West. 2024;12(2):118–125. DOI: https://doi.org/10.56871/CmN-W.2024.48.43.010

Received: 15.01.2024 **Revised: 12.03.2024** **Accepted: 05.06.2024**

Abstract. The aim of the study was to evaluate the frequency of allelic variants of the genes of predisposition to arterial hypertension in adults, 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 (NN) with gestational age >28 but ≤34 weeks (n=105), as well as a population sample of adults (n=100). For the analysis, loci with already known association with the development of arterial hypertension and coronary heart disease were selected: *AGT* (rs4762), *AGTR1* (rs5186), *ACE* (Ins\Del), *ADRB1* (rs1801253), *ADD1* (rs4961), *CYP11B2* (rs1799998), *eNOS* (rs1799983), *eNOS* (rs1549758), *eNOS* (rs2070744). The distribution of allele frequencies between the study groups was compared. Premature infants are significantly more likely to carry the allele C of the AGT gene. In newborns with ELBW, we additionally found a more frequent occurrence of mutant alleles of the *eNOS* gene and the rare GG genotype in the *ADRB1* gene. It is established that newborns with extremely low body weight, in contrast to the population of premature babies, are carriers of a greater number of risk alleles of genes predisposing to arterial hypertension.

Keywords: *premature newborns, arterial hypertension, hereditary predisposition, gene polymorphism*

ВЗАИМОСВЯЗЬ ГЕСТАЦИОННОГО ВОЗРАСТА НЕДОНОШЕННОГО НОВОРОЖДЕННОГО С НАСЛЕДСТВЕННОЙ ПРЕДРАСПОЛОЖЕННОСТЬЮ К МЕТАБОЛИЧЕСКОМУ СИНДРОМУ

Часть I. Ассоциации молекулярно-генетических предикторов артериальной гипертензии с гестационным возрастом недоношенных новорожденных

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Для цитирования: Миронов П.И., Иванов Д.О., Александрович Ю.С., Нургалиева А.Х., Валиев Р.Р., Богданова А.А., Петрова С.Г., Хуснутдинова Э.К. Взаимосвязь гестационного возраста недоношенного новорожденного с наследственной предрасположенностью к метаболическому синдрому. Часть I. Ассоциации молекулярно-генетических предикторов артериальной гипертензии с гестационным возрастом недоношенных новорожденных // Children's Medicine of the North-West. 2024. Т. 12. № 2. С. 118–125. DOI: https://doi.org/10.56871/CmN-W.2024.48.43.010

Поступила: 15.01.2024 **Одобрена: 12.03.2024** **Принята к печати: 05.06.2024**

Резюме. Цель работы — оценка частоты носительства аллельных вариантов генов, предрасположенности к артериальной гипертензии взрослых в зависимости от срока гестации недоношенного новорожденного. Дизайн исследования: проспективное, контролируемое, одноцентровое, нерандомизированное. Изучались образцы геномной ДНК у новорожденных детей с экстремально низкой массой тела (ЭНМТ) и гестационным возрастом ≤28 недель (n=95), недоношенных новорожденных (НН) с гестационным возрастом >28 но ≤34 недель (n=105), а также популяционной выборки взрослых (n=100). Для анализа были выбраны локусы с уже известной ассоциацией с развитием артериальной гипертензии и ишемической болезнью сердца: *AGT* (rs4762), *AGTR1* (rs5186), *ACE* (Ins\Del), *ADRB1* (rs1801253), *ADD1* (rs4961), *CYP11B2* (rs1799998), *eNOS* (rs1799983), *eNOS* (rs1549758), *eNOS* (rs2070744). Проводилось сравнение распределения частот аллелей и генотипов между исследуемыми группами лиц. Недоношенные дети достоверно чаще являются носителями аллеля С гена *AGT*. У новорожденных с ЭНМТ дополнительно выявлена более частая встречаемость мутантных аллелей гена *eNOS* и редкого генотипа GG гена *ADRB1*. Установлено, что новорожденные с ЭНМТ, в отличие от популяции недоношенных детей, являются носителями большего числа рисковых аллелей генов предрасположенности к артериальной гипертензии.

Ключевые слова: *недоношенные новорожденные, артериальная гипертензия, наследственная предрасположенность, полиморфизм генов*

INTRODUCTION

Analysis of data on the long-term consequences of prematurity and, in particular, the associated early chronic noncommunicable diseases such as arterial hypertension (AH) and metabolic syndrome (MS) in adulthood, is one of the urgent topics of clinical research in the last decade. Historically, the focus in the development of cardiovascular diseases emphasized individual risk factors. They were identified in the Framingham Study and other longitudinal observational projects so far [1]. The traditional risk factors are hypertension, dyslipidemia, obesity, diabetes and smoking. Subsequently, other potential predictors of AH, such as inflammation and insulin resistance, were included in this list [1]. The recognition of risk factors was a significant progress that allowed to identify real clinical targets of therapeutic interventions. Subsequent studies have shown that interventions that lead to risk factor eliminating actually reduce the risk of morbidity and mortality from cardiovascular disease [2].

At the same time, subtle mechanisms of these outcomes remain poorly understood. As applied to pediatric practice, causes related to environmental factors, various aspects of the theory of "fetal programming" and genetic features of premature infants are discussed in this aspect [3, 4].

Moreover, these data quite unambiguously point to the significance of gestational age for the early onset and even mortality from cardiovascular diseases, diabetes and lung diseases among individuals [3–7]. However, not all studies show a significant relationship between prematurity and arterial hypertension in adult individuals [6]. Although hereditary predisposition to AH may play its role in the process [7].

AIM

The aim of the research was to evaluate the frequency of carrying allelic variants of genes predisposing to adult arterial hypertension in premature 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).

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 were already associated with the development of arterial hypertension and coronary heart disease were selected for analysis: *AGT* (rs4762) — angiotensinogen gene, *AGTR1* (rs5186) — angiotensin II type 1 receptor gene, *ACE* (Ins/Del) — angiotensin-converting enzyme gene, *ADRB1* (rs1801253) — β1-adrenoreceptor gene, *ADD1* (rs4961) — gene of alpha-subunit of adducin protein, *CYP11B2* (rs1799998) — gene of cytochrome P450 second polypeptide, *eNOS* (rs1799983) — gene of nitric oxide synthase, *eNOS* (rs1549758), *eNOS* (rs2070744).

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 arterial hypertension susceptibility 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 genes *AGTR1* (rs5186), *ACE* (Ins-Del), *ADRB1* (rs1801253) gene, *eNOS* (rs1799983, rs1549758 and rs2070744), *ADD1* (rs4961), *CYP11B2* (rs1799998).

At the same time, there were statistically significant differences in the distribution of allele frequencies (p=0.0002) of the polymorphic locus rs4762 (Thr174Met) in the *AGT* gene between samples of preterm newborns and controls. There was performed an analysis of statistically significant differences in the frequency distribution of the homozygous recessive genotype of *AGT* (rs4762) among the studied groups. The C allele and CC genotype (according to the recessive inheritance model) were shown to be significantly more frequent in newborns with PN than in controls (84.2% vs 71% and 69.3 vs 46%, respectively) — χ^2=14.31; p=0.0002; odds ratio 2.17; 95% confidence interval 1.45–3.26 and χ^2=15.33; p=9.0E-5; OR 2.66; 95% CI 1.62–4.36.

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

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

Таблица 2. Сравнительный анализ распределения частот аллелей полиморфных локусов генов предрасположенности к артериальной гипертензии 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
Ген AGT (rs4762) Аллель *C* / Gene *AGT* (rs4762) Allele *C*	0.842	0.710	14.31	**0.0002**	2.17	1.45–3.26
Ген AGT (rs4762) Аллель *T* / Gene AGT (rs4762) Allele *T*	0.158	0.290			0.46	0.31–0.69
Ген AGTR1 (rs5186) Аллель *A*	0.766	0.790	0.43	0.51	0.87	0.58–1.32
Ген AGTR1 (rs5186) Аллель *C* / Gene *AGTR1* (rs5186) Allele *A*	0.234	0.210			1.15	0.76–1.73
Ген ACE (Ins\Del) Аллель *I* / Gene *ACE* (Ins\Del) Allele *I*	0.540	0.585	1.08	0.3	0.83	0.59–1.18
Ген ACE (Ins\Del) Аллель *D* / Gene *ACE* (Ins\Del) Allele *D*	0.460	0.415			1.20	0.85–1.69
Ген ADRB1 (rs1801253) Аллель *C* / Gene *ADRB1* (rs1801253) Allele *C*	0.802	0.798	0.01	0.92	1.02	0.67–1.56
Ген ADRB1 (rs1801253) Аллель *G* / Gene *ADRB1* (rs1801253) Allele *G*	0.198	0.202			0.98	0.64–1.50
Ген eNOS rs1799983 Аллель *G* / Gene *eNOS* rs1799983 Allele *G*	0.770	0.750	0.30	0.58	1.12	0.75–1.66
Ген eNOS rs1799983 Аллель *T* / Gene *eNOS* rs1799983 Allele *T*	0.230	0.250			0.90	0.60–1.33
Ген eNOS rs1549758 Аллель *C* / Gene *eNOS* rs1549758 Allele *C*	0.763	0.760	0.01	0.94	1.01	0.68–1.51
Ген *eNOS* rs1549758 Аллель *T* / Gene *eNOS* rs1549758 Allele *T*	0.237	0.240			0.99	0.66–1.47
Ген *eNOS* rs2070744 Аллель *T* / Gene *eNOS* rs2070744 Allele *T*	0.676	0.725	1.51	0.22	0.79	0.54–1.15
Ген eNOS rs2070744 Аллель *C* / Gene *eNOS* rs2070744 Allele *C*	0.324	0.275			1.26	0.87–1.84
Ген *ADD1 rs4961* Аллель *G* / Gene *ADD1 rs4961* Allele *G*	0.774	0.835	2.96	0.09	0.68	0.43–1.06
Ген *ADD1 rs4961* Аллель *T* / Gene *ADD1 rs4961* Allele *T*	0.226	0.165			1.48	0.95–2.30
Ген *CYP11B2 rs1799998* Аллель *T* / Gene *CYP11B2 rs1799998* Allele *T*	0.492	0.515	0.27	0.6	0.91	0.65–1.28
Ген *CYP11B2 rs1799998* Аллель *C* / Gene *CYP11B2 rs1799998* Allele *C*	0.508	0.485			1.10	0.78–1.54

Subsequently, a comparative analysis was performed in order to note the differences between allele frequency distribution of the same genes among a population-based sample of adults and ELBW (Table 3).

Analyzing the data in Table 3, it may be noted that there were statistically significant differences in the distribution of allele frequencies (p=0.0007) of the polymorphic locus rs4762 (Thr174Met) in the *AGT* gene between the samples of ELBW and controls, which is similar to the general group of premature infants. In addition, it was found that CC genotype (according to recessive inheritance model) was significantly more frequent in ELBW

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

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

Аллели / Alleles	Случаи / Cases (n=105)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Ген *AGT* (rs4762) Аллель *C* / Gene *AGT* (rs4762) Allele *C*	0.853	0.710	11.53	**0.0007**	2.36	1.43–3.91
Ген *AGT* (rs4762) Аллель *T* / Gene *AGT* (rs4762) Allele *T*	0.147	0.290			0.42	0.26–0.70
Ген *AGTR1* (rs5186) Аллель *A* / Gene *AGTR1* (rs5186) Allele *A*	0.805	0.790	0.14	0.71	1.10	0.67–1.80
Ген AGTR1 (rs5186) Аллель *C* / Gene *AGTR1* (rs5186) Allele *C*	0.195	0.210			0.91	0.55–1.49
Ген *ACE* (Ins\Del) Аллель *I* / Gene *ACE* (Ins\Del) Allele *I*	0.511	0.585	2.18	0.14	0.74	0.50–1.10
Ген *ACE* (Ins\Del) Аллель *D* / Gene *ACE* (Ins\Del) Allele *D*	0.489	0.415			1.35	0.91–2.02
Ген *ADRB1* (rs1801253) Аллель *C* / Gene *ADRB1* (rs1801253) Allele *C*	0.758	0.798	0.90	0.34	0.79	0.49–1.28
Ген *ADRB1* (rs1801253) Аллель *G* / Gene *ADRB1* (rs1801253) Allele *G*	0.242	0.202			1.26	0.78–2.04
Ген *eNOS* rs1799983 Аллель *G* / Gene *eNOS* rs1799983 Allele *G*	0.862	0.750	7.68	**0.006**	2.08	1.23–3.51
Ген *eNOS* rs1799983 Аллель *T* / Gene *eNOS* rs1799983 Allele *T*	0.138	0.250			0.48	0.29–0.81
Ген eNOS rs1549758 Аллель *C* / Gene *eNOS* rs1549758 Allele *C*	0.851	0.760	5.10	**0.02**	1.80	1.08–3.02
Ген *eNOS* rs1549758 Аллель *T* / Ген *eNOS* rs1549758 Аллель *T*	0.149	0.240			0.55	0.33–0.93
Ген *eNOS* rs2070744 Аллель *T* / Gene *eNOS* rs2070744 Allele *T*	0.697	0.725	0.38	0.54	0.87	0.56–1.35
Ген *eNOS* rs2070744 Аллель *C* / Gene *eNOS* rs2070744 Allele *C*	0.303	0.275			1.15	0.74–1.78
Ген *ADD1* rs4961 Аллель *G* / Gene *ADD1* rs4961 Allele *G*	0.791	0.835	1.21	0.27	0.75	0.45–1.26
Ген *ADD1* rs4961 Аллель *T* / Gene *ADD1* rs4961 Allele *T*	0.209	0.165			1.34	0.80–2.24
Ген *CYP11B2* rs1799998 Аллель *T* / Gene *CYP11B2* rs1799998 Allele *T*	0.544	0.515	0.32	0.57	1.12	0.75–1.68
Ген CYP11B2 rs1799998 Аллель *C* / Gene *CYP11B2* rs1799998 Allele *C*	0.456	0.485			0.89	0.60–1.33

than in controls (85.53% vs 71% and 70.5 vs 46%, respectively) — χ^2=11.53; p=0.0007; OR 2.36; 95% CI 1.43–3.91 and χ^2=12.03; p=0.0005; OR 2.81; 95% CI 1.56–5.07. In addition, TT genotype was more often detected in the population sample compared to ELBW (p=0.05).

Allele and genotype frequencies of polymorphic loci in genes *AGTR1* (rs5186), *ACE* (Ins-Del), *ADRB1* (rs1801253), *ADD1* (rs4961) and *CYP11B2* (rs1799998) were not statistically significant (p >0.05). At the same time, when comparing the genotype frequency distribution of the polymorphic locus in ADRB1

(rs1801253) between the studied groups, it was shown that the GG genotype, which was homozygous for a rare allele, was more frequently detected in ELBW (4.2% of cases) compared to the population control (not detected) — χ^2=4.27; p=0.04; OR 9.79; 95% CI 0.52–18.43. Statistically significant differences were found in the distribution of allele frequencies (p=0.006) and genotypes (p=0.02) of the polymorphic locus in eNOS (rs1799983) between the ELBW group and controls. The G allele was significantly more frequent in newborns with ELBW than in controls (86.2% vs 75.0%) — χ^2=7.68; p=0.006; OR 2.08; 95% CI 1.23–3.51. Whereas the T allele was significantly less frequent among newborns with ELBW compared to the population average (13.8% vs 25.0%) — χ^2=7.68; p=0.006; RR 0.48; 95% CI 0.29–0.81. The GG genotype also appeared to be more frequently detected in the ELBW group (73.4% vs 56.0) — χ^2=6.40; p=0.01; OR 2.17; 95% CI 1.18–3.97. Statistically significant differences in allele frequency distribution (p=0.02) and *eNOS* (rs1549758) were found between samples of neonates with extremely low birth weight and controls. The C allele was shown to be significantly more frequent in children with ENMT as compared to control (85.1% vs 76.0%) — χ^2=5.10; p=0.02; OR 1.80; 95% CI 1.08–3.02. Whereas the T allele was significantly less frequent among neonates with ELBW than the population average (14.9% vs 24.0%) — χ^2=5.10; p=0.02; OR 0.55; 95% CI 0.33–0.93. The CC genotype was also more frequently detected in the ELBW group (72.3% vs 57.0) — χ^2=4.98; p=0.03; OR 1.97; 95% CI 1.08–3.60.

No statistically significant differences (p >0.05) were found in distribution of allele and genotype frequencies of the polymorphic locus in eNOS (rs2070744) between groups.

DISCUSSION

The aim of the research was to determine that increased incidence of cardiovascular disease in adulthood may be related to hereditary predisposition in individuals born prematurely. In addition, gestational age was proposed to have some relevance as well as.

Indeed, it was found that preterm infants were significantly more likely to be carriers of the C allele, gene *AGT*. *AGT* encodes a protein angiotensinogen, from which angiotensin I is formed under the action of renin, which is actively involved in regulation of systemic blood pressure [8].

Moreover, the research revealed that ELBW have more pronounced features of patient's genotype predisposition to arterial hypertension. This contingent of patients also had a higher frequency of risk polymorphic alleles of *eNOS* and a rare GG genotype of *ADRB1*. *eNOS3* encodes a nitric oxide synthase enzyme, which produces nitric oxide (NO). Inhibition of NO synthase usually leads to prolonged arterial hypertension [8]. *ADRB1* is a gene of β1-adrenoreceptor, it encodes protein which is a target for beta-blockers. Therefore, the extent to which a drug helps to reduce high blood pressure partially depends on polymorphic loci of this gene [8].

On the one hand, this fact confirms the well-known paradigm that newborns with ELBW significantly differ from premature infants with normal body weight concerning their biological characteristics [9]. On the other hand, predisposition to early arterial hypertension in this contingent makes it necessary to modify approaches to strategy planning for future targeting of health care budget expenditures. In a large Swedish population-based cohort study (923,686 women) and a recent study from the USA, it was found that mothers who gave birth to preterm infants had an increased risk of cardiovascular disease in cathamnesis [10]. In addition, preterm neonates are known to have a significantly increased risk of coronary heart disease and associated mortality [11].

Indeed, our research has several limitations. It is very difficult to test the direct effect of single polymorphisms on blood pressure due to the minimal effect of each polymorphism. Assessing the joint effect of genes in relation to quantitative or qualitative phenotype, it is possible to encounter a methodological error when calculating the genetic risk index, which is defined as the total number of alleles associated with a disease [12]. It could be avoided by genome-wide association researches in preterm neonates. Ideally, such studies would have a strong contribution to analyze the monitoring of blood pressure data and endogenous influences such as cortisol levels and exogenous influences such as catecholamine dosing. This will hopefully lead to identifying the most significant genetic variants that can guide therapeutic decisions.

In addition, it should also be recalled that environmental factors may also contribute to individual clinical features of arterial hypertension. Specifics of allelic variants of polymorphic loci in ELBW parents had not been investigated in the research. Ethnic characteristics of PN had not been taken into account. Nor did we calculate the

necessary number of controls. All the above-mentioned indicates the need for further validation of the results obtained on a larger group.

CONCLUSION

The research demonstrated that neonates with extremely low birth weight, in contrast to premature neonates with normal body weight, carry a greater number of risk alleles of genes predisposing to arterial hypertension, which may increase the risk of developing AH in adulthood.

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.

Competing interests. The authors declare that they have no competing interests.

Funding source. The work supported by Ministry of Science and Higher Education of the Russian Federation (FZWU-2020–0027).

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. П.И. Миронов — концепция и дизайн исследования, обработка материала, написание статьи, анализ литературы; Ю.С. Александрович — набор и обработка материала, написание статьи; А.Х. Нургалиева — набор и обработка материала, написание статьи; Р.Р. Валиев — выполнение генетических исследований, обработка материала, написание статьи, анализ литературы; А.С. Богданова — выполнение генетических исследований; С.Г. Петрова — выполнение генетических исследований; Э.К. Хуснутдинова — рецензирование интеллектуального содержимого; Д.О. Иванов — рецензирование интеллектуального содержимого. Все авторы прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работа поддержана Министерством науки и высшего образования РФ № FZWU-2020-0027.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

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