

Approaches to the diagnosis of immunodeficiency disorders in children with Down syndrome

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Abstract

Relevance. Down syndrome is one of the most common genetic diseases worldwide. People with this syndrome are at risk for developing immunodeficiency conditions. The article discusses the results of a study of TREC and KREC concentrations in children with Down syndrome.

The aim of the study was to determine the concentration of TREC and KREC in children with Down syndrome compared with healthy children.

Materials and methods. A prospective study was conducted to determine the content of TREC and KREC in the blood of children and adolescents with Down syndrome.

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Results. It was found that the concentration of TREC in children with Down syndrome is significantly lower than in healthy children of the appropriate age, which indicates a violation in the development of the T-cell link of immunity. A similar pattern is observed for KREC levels, which indicates a violation of the maturation of B-lymphocytes responsible for the synthesis of antibodies.

Conclusion. This study highlights the importance of early diagnosis and monitoring of the immune status in children with Down syndrome by determining the concentration of TREC and KREC, which will allow timely corrective measures and prevent the development of complications.

Keywords: Down syndrome, TREC, KREC, immunodeficiency states

Conflict of interests:

The authors declare no conflict of interest.

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Подходы к диагностике иммунодефицитных состояний у детей с синдромом Дауна

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Резюме статьи

Актуальность. Синдром Дауна является одним из самых распространенных генетических заболеваний во всем мире. Люди с данным синдромом находятся в группе риска по развитию иммунодефицитных состояний. В статье рассматриваются результаты исследования концентрации TREC и KREC у детей с синдромом Дауна.

Цель исследования: определение концентрации TREC и KREC у детей с синдромом Дауна в сравнении со здоровыми детьми.

Материалы и методы. Проведено проспективное исследование, направленное на определение содержания TREC и KREC в крови детей и подростков с синдромом Дауна.

Результаты. Установлено, что концентрация TREC у детей с синдромом Дауна значительно ниже по сравнению со здоровыми детьми соответствующего возраста, что указывает на нарушение в развитии Т-клеточного звена иммунитета. Аналогичная картина наблюдается и для уровней KREC, что свидетельствует о нарушении созревания В-лимфоцитов, отвечающих за синтез антител.

Заключение. Данное исследование подчеркивает важность ранней диагностики и мониторинга иммунного статуса у детей с синдромом Дауна путем определения концентрации TREC и KREC, что позволит своевременно проводить коррекционные мероприятия и предотвращать развитие осложнений.

Ключевые слова: синдром Дауна, TREC, KREC, иммунодефицитные состояния

Конфликт интересов:

Авторы заявляют об отсутствии конфликта интересов.

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RELEVANCE. Down syndrome is one of the most common genetic disorders. In Russia, the incidence of newborns with Down syndrome is 8.27 per 10,000 births [1]. In the Nizhny Novgorod region, between 2014 and 2023, the average incidence of Down syndrome among newborns was 8.7 per 10,000 births [2]. Down syndrome is characterized by phenotypic features, multiple abnormalities of the cardiovascular, central nervous, and immune systems, the gastrointestinal tract, and the musculoskeletal system, with respiratory tract diseases being very common [3]. This group of children is prone to frequent infections, including upper and lower respiratory tract infections [4]. This may be associated with the overexpression of genes encoded by the 21st chromosome, which determines the characteristics of the immune status in people with Down syndrome, manifested, among other things, by a decrease in the number of lymphocytes [5]. There may be a decrease in the T-cell response and the number of immunoglobulins [6]. A number of studies have revealed age-related patterns in the functioning of the immune system: T and B cells are significantly reduced at a young age and increased with aging. According to G. Ram, T and B cells are reduced to less than 10% of normal levels

in almost 90% of children with Down syndrome and to less than 5% in 60% of them [7].

Currently, most studies have shown that immunological deficiency in patients with Down syndrome is mainly caused by impaired thymus function, which leads to a decrease in the number of lymphocytes, a reduction in the cortical layer, loss of differentiation between the cortical and medullary layers, and hypertrophy of the medullary layer of the thymus with Hassall's corpuscles. Impaired thymus maturation causes phenotypic and functional defects in circulating T lymphocytes [8]. It should be noted that a number of congenital heart defects require surgical treatment, which, in turn, is performed with partial thymectomy.

Children with Down syndrome have a decrease in the number of T lymphocytes (CD3⁺) with an increase in CD4⁺, CD8⁺ cells, the absolute number of B lymphocytes (CD20⁺), the number of activated cells (CD25⁺) and natural killer cells (CD16⁺), which may be a compensatory reaction of the immune system. They also show a significant decrease in total IgG, a tendency toward a decrease in IgM, and no change in IgA levels. The decrease in IgM and IgG levels, combined with a reduction in the number of T and

B cells, predetermines frequent morbidity and a low level of immune response. A decrease in the number of T-lymphocytes (CD3⁺) and an increase in CD4⁺, CD8⁺ subpopulations and the absolute number of B cells (CD20⁺) are the hallmarks of this syndrome [9].

TREC and KREC are DNA fragments formed as a result of the maturation of T and B lymphocytes during VJ recombination of TRA and TRD genes of the T-cell receptor and recombination of the IGK locus of light chains of B-lymphocyte immunoglobulins. TREC (T-cell receptor excision circle) are ring-shaped DNA fragments formed in the thymus in naive T lymphocytes during VJ recombination of the TRA and TRD genes of the corresponding receptor. Their presence indicates T-cell maturation. KREC (kappa-deleting recombination excision circle) are ring-shaped DNA segments formed in B cells during their maturation in the bone marrow [10]. The use of TREC and KREC quantitative assessment is gradually expanding and can be used to diagnose primary immunodeficiency diseases (PID). These indicators are especially important for children with Down syndrome, as they often have various immune disorders [11]. Quantitative analysis of TREC/KREC cells is a relatively new and sensitive marker of thymus function, which can provide information about the condition of the organ in various pathological states, as well as its ability to generate new T cells.

STUDY OBJECTIVE: To determine TREC and KREC concentrations in children with Down syndrome compared to healthy children.

MATERIALS AND METHODS. A prospective study of TREC and KREC concentrations in whole blood in children with Down syndrome was conducted at the Nizhny Novgorod Regional Children's Clinical Hospital.

127 children were examined. Two groups were identified: the main group and the control group. The main group included children with Down syndrome confirmed by genetic testing — 63 children. The control group consisted of children from health groups 1 and 2 — 64 children. Each group was divided

into subgroups by age: subgroup 1—0 to 11 months, subgroup 2—1 to 5 years, subgroup 3—6 to 17 years, subgroup 4—over 18 years. The main group consisted of 11 people aged 0–11 months, 22 aged 1–5 years, 26 aged 6–17 years, and 4 aged over 18 years. The control group included 12 children aged 0–11 months, 22 aged 1–5 years, 26 aged 6–17 years, and 4 over 18 years of age.

The main group and the control group were comparable in terms of age. For the main group, the average age was 1 month [6 days; 11 months] for the 0–11month subgroup; 2 years 8 months [1 year; 5 years] for the 1–5year subgroup; 6–17 years — 10 years [6 years; 17 years]; over 18 years — 20 years [18 years; 23 years]. For the control group, the average age was 2 months [6 days; 11 months] for the 0–11month subgroup; 1–5 years — 3 years [1 year; 5 years]; 6–17 years — 10 years [6 years; 17 years]; over 18 years — 21 years [18 years; 23 years].

During the examination, the patient's medical history is analyzed, a physical examination is performed, and examinations are conducted by specialists such as a cardiologist, endocrinologist, hematologist, otolaryngologist, ophthalmologist, orthopedic traumatologist, allergist-immunologist, neurologist, as well as laboratory tests: determination of TREC and KREC concentrations.

Quantitative assessment of TREC and KREC was performed using quantitative real-time PCR analysis with Immuno-Bit test systems (Immuno-Bit LLC Reagent kit for the isolation and quantitative determination of TREC and KREC DNA by real-time polymerase chain reaction) (ABV-TEST LLC, Russia). The principle of the method is based on the quantitative determination of the content of TREC and KREC DNA copies using the amplification of TREC and KREC DNA segments with primers specific to these segments and Taq DNA polymerase, followed by the determination of the accumulation of a specific fluorescent signal on the amplifier with a real-time fluorescent signal detection system. The threshold values of this TREC copy test system for 10⁵ nucleated cells (leukocytes) depending on age: 0–1 year — more than 200, 1–6 years — more than 80, 6–18 years — more than 30. The threshold values for KREC copies per 10⁵ nucleated cells (leu-

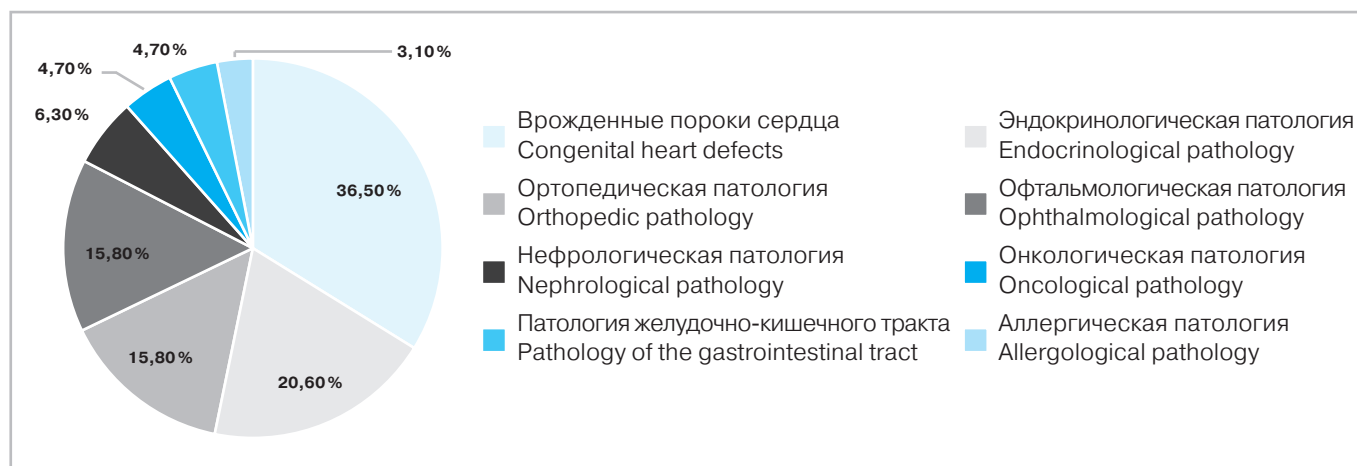


Fig. 1. Somatic pathology in the main group (author's figure)

Рис. 1. Соматическая патология в основной группе (рисунок автора)

kocytes) depending on age: 0–1 year — more than 250, 1–6 years — more than 100, 6–18 years — more than 40. To extract DNA from whole human blood, the “Reagent kit for DNA extraction from clinical material based on alcohol precipitation (“Extra-DNA-Bio”) according to TU 9398-244-98539446-2012” was used, RU No. FSR 2012/13631, manufactured by AlcorBio LLC.

A one-way analysis of variance was performed to determine the concentration of TREC and KREC in whole blood in different age subgroups. Statistical processing was performed using IBM SPSS Statistics software.

STUDY RESULTS. In the main group, 23 patients were diagnosed with congenital heart defects (36.5%), endocrine system pathology (au-

toimmune thyroiditis) in 13 patients (20.6%), orthopedic pathology (clubfoot, valgus foot deformity, scoliosis) in 15.8%, and ophthalmic pathology (astigmatism, amblyopia) in 10 patients (15.8%) (Fig. 1).

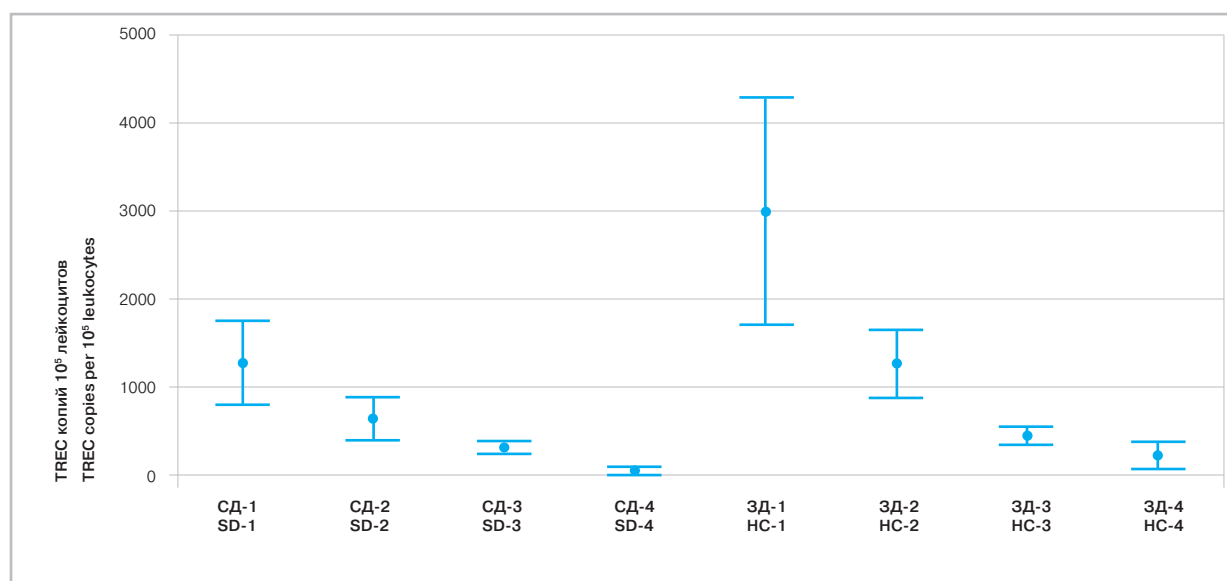
The gender distribution of study participants in the main group and control group is presented in Table 1. Gender differences between groups are statistically insignificant ($p > 0.05$).

When performing a one-factor analysis of variance in groups of children with Down syndrome and healthy children aged 0–11 months, the TREC content in whole blood in children in the main group ranged from 855 to 1693 copies per 10^5 leukocytes, with a median of 1228 copies per 10^5 leukocytes (95% CI 750–1758 copies per 10^5 leukocytes), while the TREC content in whole blood in children in the

Table 1. Gender structure of the surveyed (author's table)

Таблица 1. Гендерная структура обследуемых (таблица автора)

Возраст Age	Основная группа The main group			Контрольная группа The control group		
	Абс. число детей The absolute number of children	Абс. число девочек The absolute number of girls	Доля девочек, % The proportion of girls, %	Абс. число детей The absolute number of children	Абс. число девочек The absolute number of girls	Доля девочек, % The proportion of girls, %
0–11 мес. 0–11 mos.	11	6	54%	12	6	50%
1–5 лет 1–5 years old	22	9	41%	22	8	36%
6–17 лет 6–17 years old	26	12	46%	26	14	53%
18 лет и старше 18 years and older	4	2	50%	4	2	50%



СД — дети с синдромом Дауна, DS — children with Down syndrome

ЗД — условно здоровые дети, НС — conditionally healthy children

1. Возраст: 0–11 месяцев
Age: 0–11 months

2. Возраст: 1–5 лет
Age: 1–5 years old

3. Возраст: 6–17 лет
Age: 6–17 years old

4. Возраст: 18 и старше
Age: 18 and older

Fig. 2. TREC content in whole blood of children of the main group and the control group of different ages (author's figure)

Рис. 2. Содержание TREC в цельной крови детей основной группы и контрольной группы разного возраста (рисунки автора)

control group ranged from 1852 to 4145 copies per 10^5 leukocytes, with a median of 2412 copies per 10^5 leukocytes (95% CI 1711–4286 copies per 10^5 leukocytes), which is 2 times higher than in the main group, $p = 0.01$.

For the age of 1–5 years, the TREC concentration in children in the main group was 413–867 copies per 10^5 leukocytes, with a median of 585 copies per 10^5 leukocytes (95% CI 398–883 copies per 10^5 leukocytes), while the TREC content in children in the control group of the same age was 896–1632 copies per 10^5 leukocytes, with a median of 1156 copies per 10^5 leukocytes (95% CI 874–1655 copies per 10^5 leukocytes), $p = 0.008$.

In children aged 6–17 years, the TREC concentration in the main group was 102–239 copies per 10^5 leukocytes, with a median of 88 copies per 10^5 leukocytes (95% CI 98–242 copies per 10^5 leukocytes), while the TREC content in whole blood in children in the control group was 344–541 copies per 10^5 leukocytes, with a median of 400 copies per 10^5 leukocytes (95% CI 339–546 copies per 10^5 leukocytes), which is 4.5 times higher than in the main group, $p = 0.01$.

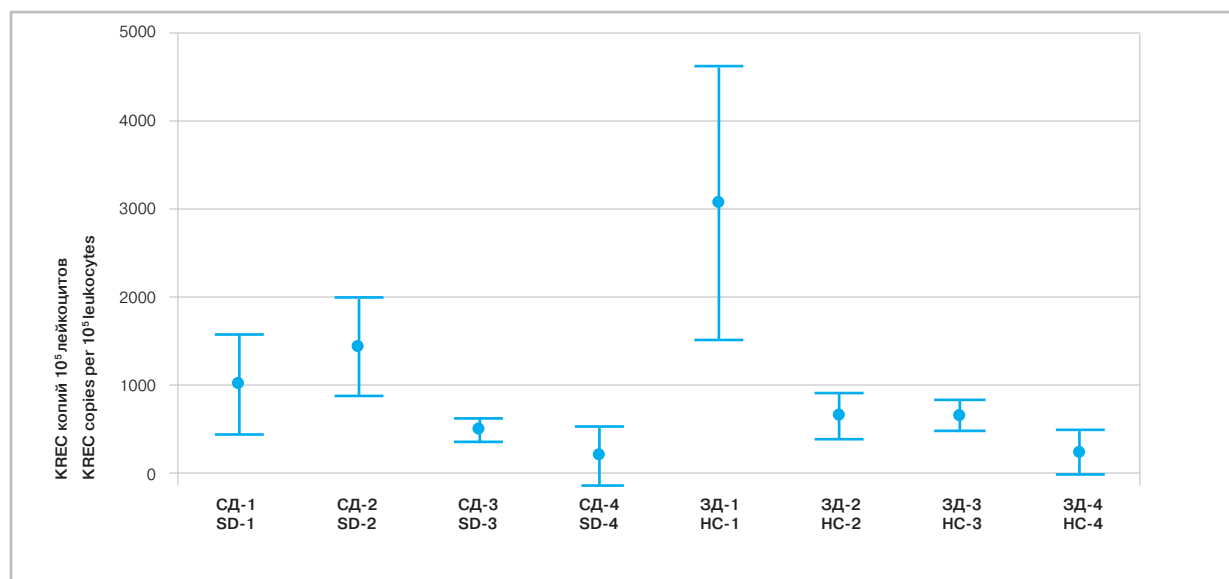
In young people of the main group aged 18 and older, TREC was 8 times lower than in the control

group and amounted to 10–71 copies per 10^5 leukocytes, with a median of 42.5 copies per 10^5 leukocytes (95% CI 8–90 copies per 10^5 leukocytes), $p = 0.009$, while in young people in the control group aged 18 and older, TREC was 132–315 copies per 10^5 leukocytes, with a median of 207 copies per 10^5 leukocytes, which is 5 times higher than in the main group, $p = 0.009$.

Statistically significant differences between the main group and the control group were identified in all age groups (Fig. 2).

When performing a one-factor analysis of variance in groups of children with Down syndrome and healthy children, the distribution of KREC content in whole blood in children with Down syndrome aged 0–11 months was in the range of 523–1511 copies per 10^5 leukocytes, with a median of 869 copies per 10^5 leukocytes (95% CI 447–1587 copies per 10^5 leukocytes), while in healthy children aged 0–11 months, the values ranged from 2738 to 4452 copies per 10^5 leukocytes, median — 2738 copies per 10^5 leukocytes (95% CI 1517–4622 copies per 10^5 leukocytes), $p = 0.01$.

At the age of 1–5 years, the concentration of KREC in the main group ranged from 371 to 627 copies per 10^5 leukocytes, with a median of 520 copies per 10^5



СД — дети с синдромом Дауна, DS — children with Down syndrome

ЗД — условно здоровые дети, HC — conditionally healthy children

1. Возраст: 0–11 месяцев
Age: 0–11 months

2. Возраст: 1–5 лет
Age: 1–5 years old

3. Возраст: 6–17 лет
Age: 6–17 years old

4. Возраст: 18 и старше
Age: 18 and older

Рис. 3. Содержание KREC в цельной крови детей основной группы и контроля разного возраста (рисунок автора)

Fig. 3. KREC content in whole blood of children of the main group and control of different ages (author's figure)

leukocytes (95% CI 363–636 copies per 10⁵ leukocytes), while the KREC concentration in children in the control group of the same age was 1032–2001 copies per 10⁵ leukocytes, with a median of 1447 copies per 10⁵ leukocytes (95% CI 1002–2031 copies per 10⁵ leukocytes), which is 3 times higher than in the main group, $p = 0,005$.

In children of the main group aged 6–17 years, the concentration of KREC was 21 times lower than in the control group, which, respectively, amounted to 12–329 units, median — 131 copies per 10⁵ leukocytes (95% CI 153–487 copies per 10⁵ leukocytes) versus 494–827 copies per 10⁵ leukocytes, the median was 604 copies per 10⁵ leukocytes (95% CI 486–835 copies per 10⁵ leukocytes) in the control group, $p = 0,005$.

In young people in the main group aged 18 and older, the KREC content was 1–408 copies per 10⁵ leukocytes, with a median of 160 copies per 10⁵ leukocytes (95% CI 124–535 copies per 10⁵ leukocytes). In the control group aged 18 and older, the KREC concentration was 67–380 copies per 10⁵ leukocytes, which was 30 times higher than in the main group, with a median of 217 copies per 10⁵ leukocytes, $p = 0,04$ (fig. 3).

DISCUSSION. Trisomy 21, widely known as Down syndrome, manifests as a complex disorder affecting multiple organs and systems, requiring a comprehensive multidisciplinary approach to monitoring and treatment [12].

An analysis of somatic pathology in children with Down syndrome showed that the frequency of somatic pathology detected in children with Down syndrome largely corresponds to other large foreign studies [13]. The most common pathologies in this study were congenital heart defects and endocrine pathology. Congenital heart defects among children with Down syndrome occurred at a frequency of 36.5%, which corresponds to the literature data on the prevalence of congenital heart defects in children with Down syndrome up to 50% [14, 15]. The frequency of endocrine pathology, primarily due to autoimmune thyroiditis, was 20.6%. This determines the importance of regular examination of children with Down syndrome for the presence of endocrine system pathology, in particular the thyroid gland, from birth [16].

TREC and KREC are used to assess the level of T- and B-lymphocytes. Changes in their concentration were detected among patients with Down

syndrome. We found that children with Down syndrome had significantly lower TREC and KREC levels compared to the control group. The results obtained are consistent with the studies by Verstegen R.H., Prada N., and Marcovecchio G.E. [17–19]. This indicates a disruption in the maturation of T and B cells in patients with Down syndrome, which underlies immunodeficiency and increased susceptibility to infections in people with this syndrome. It should be noted that, according to Eissa E. [20], no significant differences in the number of TREC and KREC copies were found between patients with and without Down syndrome, which the author himself attributes to the limited sample size.

CONCLUSION. Analysis of the data obtained showed that children with Down syndrome have lower concentrations of TREC and KREC than

healthy children in all age categories. Moreover, with age, there is a progressive decrease in TREC and KREC levels in children with Down syndrome, which is associated with the peculiarities of their immune system. As a result, these children are susceptible to various infections and autoimmune diseases. Determining TREC and KREC levels allows for the early diagnosis of immune disorders, and early diagnosis facilitates timely corrective measures and prevents the development of infectious complications.

The identified changes in the studied indicators determine the need to use TREC and KREC as molecular markers for the immunological assessment of such patients. The results also emphasize the importance of considering age-related changes in the immunological profile of such patients when interpreting immunological data. However, large-scale studies are needed to confirm these results.

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THE AUTHORS' CONTRIBUTION TO THE WORK

Anna Yu. Chirkova, Ekaterina G. Novopoltseva — creating a research concept, conducting an experimental study, analyzing and summarizing the research results, working with the text of the manuscript.

Kirill Yu. Ozhgikhin — work with literature, conducting experimental research, analyzing and summarizing the research results.

Alla A. Tarasova — creation of the research concept.

Alina S. Veselova, Ivan D. Morozov, Uliana A. Klokova — work with literature, conducting experimental research, work with the text of the manuscript.

Evgenia Yu. Baskakova, Elena M. Kozlova, Evgenia E. Larionova — analysis and synthesis of research results.

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Maria A. Pakhomova, Anastasia N. Krylova — work with literature, conducting experimental research.

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