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Clinical and genetic characteristics of patients' cohort with type 5 distal arthrogryposis caused by heterozygous variants in the *PIEZO2* gene

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Pathogenic heterozygous variants in the *PIEZO2* gene cause distal arthrogryposis type 5 – a rare autosomal dominant disease, which is characterized by the development of congenital contractures, ophthalmoparesis, ptosis and restrictive respiratory disorders. We have presented clinical and genetic characteristics of seven Russian patients with distal arthrogryposis type 5 caused by previously described and newly identified nucleotide variants in the *PIEZO2* gene. It was shown that the most severe clinical manifestations were found in patients with newly identified nucleotide variants c.8238G>A (p.Trp274Ter) and c.7095G>T (p.Trp2365Cys), while in patients with other previously described variants c.8181_8183delAGA (p.Glu2727del) and c.2134A>G (p.Met712Val) the clinical phenotype is more moderately expressed. The dynamics of phenotype formation were also noted. It has been shown that the disease progression may occur as the child grows and requires monitoring of this group of patients.

Keywords: distal arthrogryposis type 5, mechanosensitive ion channel, *PIEZO2* gene

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Background

Distal arthrogryposis (DA) type 5 is a rare autosomal dominant disease resulting from pathogenic variants in the *PIEZO2* gene (Piezo Type Mechanosensitive Ion Channel Component 2, OMIM: 613629). The gene is located on chromosome 18p11.22 and contains of 52 exons. The size of its main transcript (ENST00000503781.7) is 8,259 bp. The protein product of the gene consists of 2,752 amino acids and is a component of one of the mechanosensitive nonselective cation channels permeable to calcium ions. It functions in dorsal ganglia consisting of a heterogeneous group of peripheral sensory neurons and limited types of epithelial cells [1–4]. This channel opens when it exposed to various mechanical stimuli leading to stretching and curvature of the cell membrane; as a result of the functioning of the channel, mechanical energy is converted into electrical signals, that is, mechanical transduction occurs [2, 5]. It is known that mechanotransduction is important for biological processes such as sensory perception and embryonic development of organs, which are mediated by the mechanosensitivity of proprioceptors and the ability to transmit information along nerve fibers. The mechanical interaction between cells and the environment has been shown also to affect the speed and direction of neuronal migration in the embryonic period [6].

The OMIM catalog identifies three phenotypically similar syndromes with an autosomal dominant (AD) inheritance, for which the *PIEZO2* gene is responsible: type 3 DA (DA3, Gordon syndrome, OMIM: 114300), type 5 DA (DA5, OMIM: 108145) and Marden–Walker syndrome (MWS) (OMIM: 248700). The main clinical signs of these syndromes are congenital contractures, mainly of the distal extremities, blepharophimosis and ptosis. In addition to these signs and symptoms, DA3 patients have cleft palate and low stature, while patients with MWS suffer from mental retardation and congenital malformations of the posterior cranial fossa (Dandy–Walker malformation) [7]. The DA5 phenotype is the most common among *PIEZO2*-associated diseases. In addition to typical clinical manifestations, a significant number of patients have increased muscle

density to palpation and restrictive lung disease with the progression to pulmonary hypertension [8].

To date, it has been shown that the same pathogenic variants of the nucleotide sequence in the *PIEZO2* gene can cause all three described clinical entities and pronounced polymorphism of clinical manifestations, which can be observed in affected members of the same family. Thus, the literature discusses whether DA5, DA3, and MWS are stand alone clinical entities and suggests that differences in the spectrum and severity of their clinical manifestations may be due to the different effects of specific pathogenic variants that violate the amino acid sequence of individual domains of the Piezo2 protein [7]. So, it requires clinical and genetic correlations aimed at studying the specific clinical manifestations in patients with different types and localization of pathogenic variants in this gene. New results will not only predict the disease severity, but will also contribute to the study of its pathogenetic mechanisms.

The aim of this work was to describe the clinical and genetic characteristics of Russian patients with DA5 caused by pathogenic nucleotide variants in the *PIEZO2* gene.

Materials and methods

The sample included 7 unrelated patients living in the territory of the Russian Federation, 5 female and 2 male, aged 3 to 13 years. The diagnosis was established by a clinical examination, genealogical analysis, electromyography (EMG) and molecular genetic analysis. EMG study was performed using the Keypoint Medical System myograph (Metronic, USA).

Results

We studied the clinical and genetic characteristics of 7 patients with DA5 phenotype from unrelated families aged 3 to 13 years. In all patients, pathogenic variants in the *PIEZO2* gene were found in a heterozygous state, which made it possible to diagnose an AD inheritance. All cases are the first in the families and have *de novo* status, which was confirmed by Sanger sequencing. The clinical and genetic characteristics of the examined patients are presented in Table 1 and Fig. 1–2.

Medical history shows that pregnancy in four patients proceeded with the threatened miscarriage, fetoplacental insufficiency and oligohydramnios; in two cases, fetal ultrasound demonstrated varus foot deformity and short tubular bones. At birth, body weight deficiency (<3 %) was observed in most of the patients included in the study. One patient (4) had transient tachypnea during the newborn period, which regressed with no medical care; 2 patients (6 and 7) developed symptoms of respiratory failure requiring mechanical ventilation (patient 6 – during the day, and patient 7 – within two weeks). Variable contractures of the interphalangeal joints of the hands, restriction of movement in the wrist joints and ankle joints, flexor contractures of the elbow, knee and hip joints, bilateral varus foot deformity were found from birth, and, therefore, patients were referred to orthopedists with suspected arthrogryposis. Some of the children had dysmorphic facial features at birth (deep-set eyes, micrognathia, low-set dysplastic ears, high forehead), with muscle tightness on palpation in one case.

All patients had a physical developmental delay at the first year of life, which is associated with contractures of the interphalangeal and wrist joints, which limited arm support when crawling, and contractures of the knee and ankle joints prevented the development of independent walking skills. During their lives, the children were observed by orthopedists; all children underwent serial casting; two children underwent surgical correction of wrist joints, and three underwent achillotomy.

Clinical examination showed persistent flexor contractures of the joints of the upper and lower extremities, equino- and planovalgus foot deformity, short neck in all patients of different ages; six patients had spinal rigidity mainly in the thoracolumbar region; three patients had a funnel-shaped chest; two patients (6 and 7) had lack of growth. Due to skeletal deformities, children have formed a characteristic walking pattern, i.e., on semi-flexed legs, with support on the front edge of the foot or on toes, and a straight back. Almost all patients (6/7) had an elongation of the second toe and a shortened wide first toe. Severe restrictive lung disease worsened the condition of patient 7; lung capacity values were significantly reduced; and she was also found to have a high laryngeal standing and lack of a cartilaginous tracheal wall. Patient 6 was diagnosed with tracheal stenosis in preparation for surgery and conducting an anaesthetic support.

Muscle strength and volume of the proximal and distal arms and legs were normal in all patients. Of note, palpation revealed the increase density of all muscle groups. A number of patients has specific finding, the indurate skin of the abdomen and thighs, lumbosacral region with the formation of characteristic “lemon peel”-type pits. Also, the examination showed these pits dimples in the shoulder, elbow and wrist joints in some patients. None of the patients had disorders of superficial and deep sensitivity, as well as an increased blood creatine kinase (CK). In four patients, nerve conduction study (NCS) showed no signs of impaired conduction by motor and sensory nerve fibers; motor unit potentials were normal, with no spontaneous activity.

Symmetrical ptosis was observed in four patients, and asymmetric to the level of the middle third of the pupil in one patient (6). Restriction of upward gaze and ophthalmoparesis were observed in 6 patients; gross restriction of eye movement occurred in two patients (patients 6 and 7). Common findings were partial atrophy of the optic nerve and decreased visual acuity by an ophthalmological examination. Dysmorphic features such as a high forehead, wide eyebrows, deep-set eyes, upturned tip of the nose, triangular hypomimic face, high palate, micrognathia and dysplastic auricles were reported in almost every patient. In patient 6, a bifid uvula was detected, which is considered a characteristic sign of DA3. A delay in the early motor development was reported in all patients, but speech impairment was

Table 1. *Clinical phenotype of patients with different heterozygous variants in the PIEZO2 gene*

Parameter	Patient's number						
	1	2	3	4	5	6	7
Sex	Female	Female	Male	Male	Female	Female	Female
Age at examination (actual age), years	3 (4)	9 (10)	2 (4)	3 (3)	12 (13)	4 (4)	6 (11)
Exon	52	52	52	52	15	52	45
cDNA change	c.8181_8183del	c.8181_8183del	c.8181_8183del	c.8181_8183del	c.2134A>G	c.8238G>A	c.7095G>T
Predicted protein alteration	p.(Glu2727del)	p.(Glu2727del)	p.(Glu2727del)	p.(Glu2727del)	p.(Met712Val)	p.(Trp2746Ter)	p.(Trp2365Cys)
Pregnancy, newborn period, infancy							
Course of pregnancy	Hypamnion, threatened miscarriage	No findings	Weak fetal movement	Hypamnion, threatened miscarriage, fetoplacental insufficiency, intrauterine growth retardation 2st	No findings	Threatened miscarriage, fetoplacental insufficiency, intra-uterine growth retardation 2st	Threatened miscarriage
Birthweight (centile range, %), g	2500 (<3 %)	3100 (25–50 %)	3310 (25–50 %)	2180 (<3 %)	2600 (3 %)	1900 (<3 %)	2800 (10 %)
Respiratory disorders	–	–	–	Transient tachypnea of the newborn	–	Artificial pulmonary ventilation per day	Artificial pulmonary ventilation per 14 days
Motor development	Delayed motor development	Delayed motor development	Delayed motor development	Delayed motor development	Delayed motor development	Delayed motor development	Delayed motor development
Psycho-speech development	Psycho-speech delay	According to the age	Psycho-speech delay	According to the age	According to the age	According to the age	Psycho-speech delay
Phenotypic features							
Height (SD), sm	96 (+0,33)	131 (–0,32)	НД ND	93 (–0,73)	146 (–0,68)	90 (–2,55)	100 (–3)
Short neck	+	+	+	+	+	+	+
Ptosis	Mild, symmetrical	Mild, symmetrical	Mild, symmetrical	–	–	Moderate, asymmetrical (D >S)	Moderate, symmetrical
Ophtalmoparesis	Mild	Mild	+	–	+	Severe	Severe
Limited upward gaze	+	+	+	–	+	+	+

Continuation of table 1

Parameter	Patient's number						
	1	2	3	4	5	6	7
Ophthalmic examination	Optic nerve partial atrophy, visual acuity reduced	ND	Optic nerve partial atrophy, OD – optic pit	Hypermetropic astigmatism, visual acuity reduced	Optic nerve partial atrophy, myopic astigmatism	Visual acuity reduce	Optic nerve partial atrophy
Micrognathia	+	–	+	+	+	+	+
Highly arched palate	+	+	ND	+	+	+	+
Bilingula	–	–	ND	–	–	+	–
Dysphagia	–	–	–	–	–	–	–
Hypomimia	+	+	+	–	+	+	+
Subcutaneous fat	Pits on the external side of the shoulder, elbow, wrist joints	On the abdomen, lumbar region and gluteus thic-kened, irregularly distributed, tube-rous	Pits on the external side of the shoulder, elbow joints	–	On the abdomen, lumbar region and gluteus thickened, pits on the lumbar region	On the lumbar region and gluteus thickened, pits on the lumbar region, soft tissue pressing in the left shoulder region	On the lumbar region and gluteus thickened, pits on the lumbar region,
Hair growth changes	–	–	–	–	–	Poor in the temporal regions	Poor in the temporal regions
Intelligence	+	+	ND	+	+	+	+
Pulmonary disease	–	–	–	–	Transient atelec-tasis of one lung	Tracheal stenosis	Severe restrictive lung disease,lack of cartilaginous tracheal structure
FVC, FEV1, %	ND	62, 70 (reduced)	ND	ND	ND	ND	31, 22 (reduced)
Skeletal-muscular deformities							
Rigid spine	+	+	+	+	+	+	+
Scoliosis	–	–	–	–	–	–	–

Continuation of table 1

Parameter	Patient's number						
	1	2	3	4	5	6	7
Chest deformity	–	+	–	–	–	+	+
Contractures of the fingers, camptodactyly	+	+	+	+	+	+	+
Wrist extension limitation	+	+	+	+	+	+	+
Elbow extension limitation	+	+	+	+	+	+	+
Knee extension limitation	+	+	+	+	+	+	+
Hip extension limitation	+	+	-	+	+	+	+
Foot flexion limitation	+	+	+	+	+	+	+
Toe changes	Shortened wide va-rus deformed first toe, first toe flexion contracture	Extantion and hammer-shaped changes of the second toe	Shortened wide first toe	–	Extantion and hammer-shaped changes of the second toe	Extantion of the second toe	Extantion of the second toe
Feet deformity	Equino-flat valgus	Varus	Equino-flat valgus	Equino-flat valgus	Equino-flat valgus	Equino-flat valgus	Equino-flat valgus
Gait changes	Walks on half-bent legs, with support on the front side of the foot	Toe-walking	Walks on half-bent legs, toe-walking	Walks on half-bent legs, with support on the front side of the foot	Walks on half-bent legs, toe-walking	Walks on half-bent legs, toe-walking	Walks on half-bent legs, toe-walking
All muscles groups strength	Not reduced	Not reduced	Not reduced	Not reduced	Not reduced	Not reduced	Not reduced
Muscle tone	Reduced	Reduced	Reduced	Reduced	Reduced	Reduced	Reduced
Tendon reflexes	Brisk reflexes, ankle reflex absent	Reduced arm reflexes, patellar reflex absent, ankle reflex mild-to-moderate	ND	ND	Reduced	Brisk reflexes, ankle reflex reduced	Reduced
Muscles thickness	Increase	Increase	Increase	Increase	Increase	Increase	Increase

End of table 1

Parameter	Patient's number						
	1	2	3	4	5	6	7
Muscles pain	–	–	–	–	After physical activity	–	–
Creatine phosphokinase level, U/l	<200 (N)	<200 (N)	<200 (N)	<200 (N)	<200 (N)	<200 (N)	<200 (N)
Electroneuromyography (nerve conduction study)	Normal	Normal	Normal	ND	Normal	Normal	Normal
Needle electromyography	Normal	Normal	ND	ND	Normal	Normal	ND
Other features	–	–	–	Balanitic hypospadias	Breast asymmetry	–	An abortive form of malignant hyper-thermia during sevoran induction, epilepsy, cardiopathy

Note. *"+" – presence of a sign; "–" – absence of a sign; SD – standard deviation coefficient; FVC – forced vital capacity; FEV1 – forced expiratory volume 1-second; ND – no data.*

detected in 3 patients. Patient 7 had a history of generalized convulsive seizures, an abortive form of malignant hyperthermia during inhalation anesthesia with sevoflurane. The other abnormalities included glandular hypospadias in patient 4, and breast asymmetry in patient 5. Patients 6 and 7 had poor hair growth in the temporal regions.

Molecular genetic analysis showed 4 heterozygous variants in the *PIEZO2* gene in 7 patients, one of which was the three-nucleotide deletion of c.8181_8183delAGA (p.Glu2727del), which was described earlier [7, 9]. Another option is the nonsense variant – p.8238G>A (p.Trp274Ter), which was reported in one Russian patient [10]. Both variants are localized in the exon 52 of the gene. In another patient, a missense substitution was found in exon 15, c.2134A>G (p.Met712Val), which had previously been detected in 2 families with DA5 [7]. In the last patient, a variant c.7095G>T (p.Trp2365Cys) was identified in the 45th exon, which had not previously been described in a heterozygous state in DA patients.

Discussion

We studied the phenotypic manifestations in 7 patients with DA5 caused by four heterozygous nucleotide variants in the *PIEZO2* gene. Our cohort is advantageous as it included an analysis of patients of different ages (from 3 to 13 years) to successfully identify a number of previously undescribed phenotypic manifestations of *PIEZO2*-associated arthrogryposis, as well as to assess the formation of the disease phenotype. Specifically, signs not previously reported in publications include: uneven distribution and thickening of subcutaneous fat in the abdomen and thighs; poor temporal hair growth (in patients 6 and 7); elongated second toe and short first toe (in five patients from the entire cohort). It should be noted that, as well as in the literature, patients of our population have signs and symptoms, spectrum and the severity of which worsened as the child grew [11, 12]. For example, patient 2 (9 years old) from our population had only camptodactyly, flexor contractures of the elbow and knee joints, a narrow chest at birth, and with age, upward gaze restriction, upper lid ptosis, spinal rigidity, decreased vital capacity, limited mobility of the wrist joints, flexor contractures of the ankle joints, varus foot deformity, elongated and hammer-like second toe, indurated and unevenly distributed subcutaneous fat on the abdomen and in the lumbar region were noted. In patient 6, at the age of 3, tracheal stenosis and asymmetric upper lid ptosis were noted, and in patient 7, at the age of 3, pharmacoresistant convulsive paroxysms, malignant hyperthermia during inhalation anesthesia and restrictive lung disease occurred. These findings confirm the progressive nature of DA5, which justifies regular follow up in this cohort.

According to the HGMD database and literature data, more than 40 pathogenic variants in the *PIEZO2* gene have been identified in recent years in patients with various DA variants. Most of them are localized in 52 exons and have a dominant-negative effect, leading to slower inactivation and/or accelerated restoration of channel activity [13].

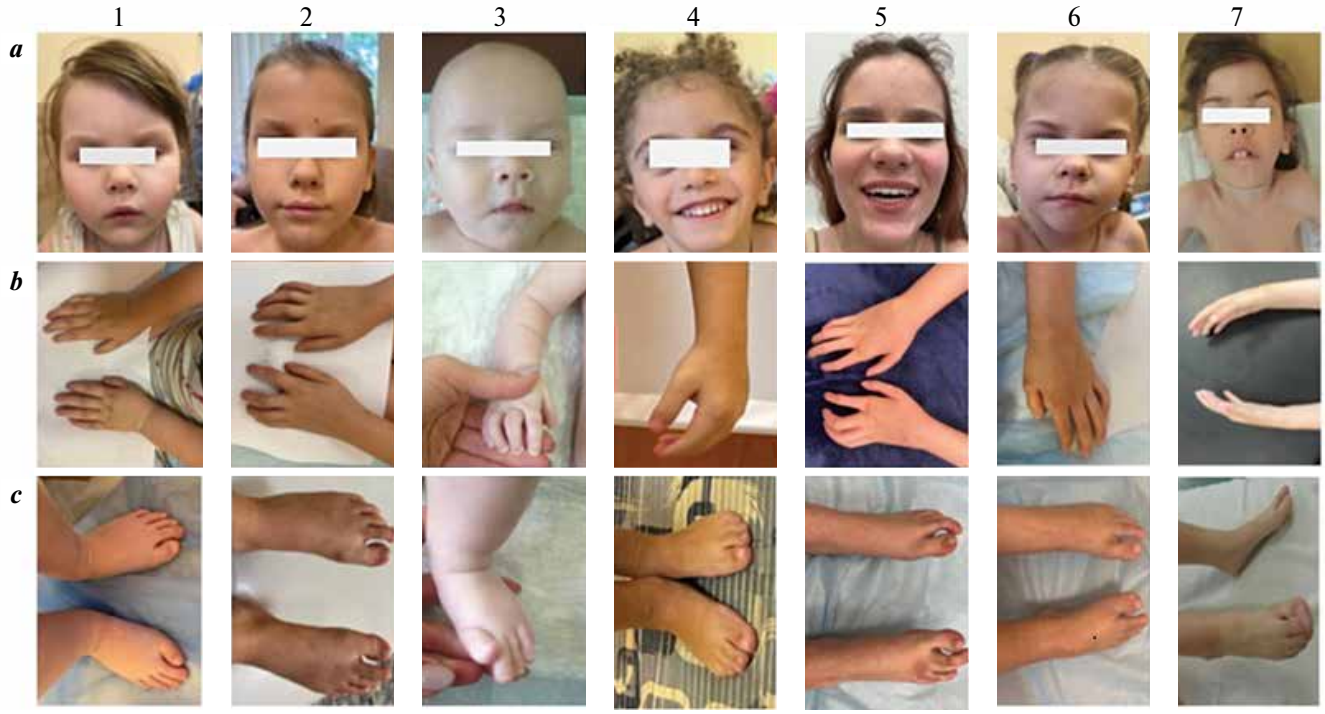

Fig. 1. *Phenotype of patients 1–7: a – facial dysmorphisms (high forehead, wide eyebrows, deep-set eyes, ptosis, upturned nasal tip, triangular hypomimic face, micrognathia); b – camptodactyly; c – equino-flat valgus feet deformity, extantion of the second toe, shortened wide first toe*

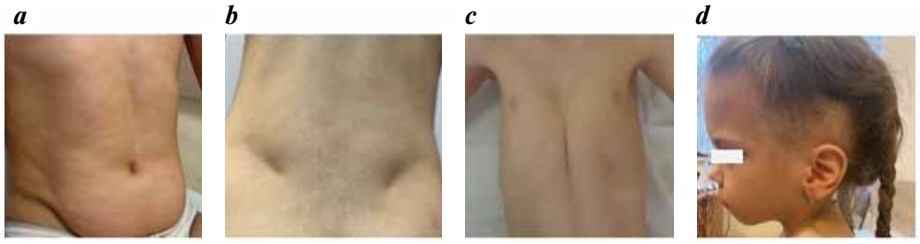

Fig. 2. *Phenotype characteristics: a – thickened and bumpy skin in the abdomen (patient 2); b – thickened skin in the lumbosacral region with the formation of symmetrical dimples (patient 6); c – foveated chest deformity (patient 7); d – poor hair growth in the temporal region, low-lying dysplatic auricles, micrognathia, upturned nasal tip, short neck (patient 6)*

In most of our patients, the previously described recurrent pathogenic variant of the nucleotide sequence in the *PIEZO2* gene was determined, leading to deletion of the glutamic amino acid at position 2727 (p.Glu2727del, NM_022068.3) without frame shift, and located in the highly conserved peptide domain of the C-terminal part of the gene [7, 9]. Using the p.Glu2727del nucleotide variant as an example, electrophysiological studies have demonstrated how it influences the biophysical properties associated with the channel functions; in particular, it causes a slower inactivation of the PIEZO2 channel and/or a more rapid recovery after inactivation, which leads to an increase in channel activity in response to a mechanical stimulus and suggests that all dominant variants are associated with increased protein function and excessive PIEZO2 activity in proprioceptive neurons impairs the development of the musculoskeletal system [9].

The other heterozygous variants identified by us in the *PIEZO2* gene included c.2134A>G, localized at the N-terminal site of the protein in domain 15, which is rare in the AD inheritance of DA5 and is more typical for autosomal recessive (AR) variants. There were no additional phenotypic features, except for the breast asymmetry and the presence of transient atelectasis of one lung, in this 12-year-old female patient. Two other variants of c.8238G>A and c.7095G>T (patients 6 and 7), located in the N-terminal region of the gene, were first described in a heterozygous state in patients with DA. These variants are associated with the most severe clinical manifestations of the disease with the formation of height and weight deficits, severe contractures and deformities of the interphalangeal and large joints of the upper and lower extremities, ophthalmoplegia, ptosis, chest deformity, restrictive lung disease, severe respiratory failure, tracheal stenosis, and with generalized seizures and malignant hyperthermia during inhalation anesthesia, as well as cardiopathy reported in the case of patient 7 with C.7095G>T variant. It should be emphasized that

variant c.7095G>T was identified in a homozygous state by a group of authors during an extensive study of several thousand inbred families from Saudi Arabia. The authors do not describe the specific clinical manifestations in a 6-year-old child with this variant, reporting only that he had hypotonia and arthrogryposis [14].

Conclusion

Our clinical and genetic analysis suggests that: children with heterozygous pathogenic variants in the *PIEZO2* gene have polymorphism of clinical manifestations, the spectrum of which depends on the localization of amino acid substitution in a protein molecule; the phenotype has been shown to change over time, i.e., as the child grows, the disease can progress and presents with contractures of large joints, restrictive respiratory tract disorders, as well as signs and symptoms of nervous system involvement, which should be subjects for high clinical suspicion. In addition, when interpreting the results of molecular genetic analysis, one may consider the AR inheritance of DA, the symptoms of which in early childhood may be similar to AD variants of the disease [15, 16].

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Authors' contributions
E.L. Dadali, E.A. Melnik: research design development, obtaining and analyzing data, reviewing publications on the topic of the article, writing the article;
T.V. Markova, S.S. Nikitin: obtaining and analyzing data, reviewing publications on the topic of the article, editing the article;
I.V. Sharkova, O.V. Chalanskaya, L.A. Bessonova, E.A. Shestopalova, S.I. Trofimova, O.E. Agranovich: obtaining and analyzing data;
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