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MEDICO-GEOGRAPHICAL ANALYSIS OF FREQUENT CONGENITAL MALFORMATIONS IN NEWBORNS IN THE PERIOD FROM 2007 TO 2020 IN THE REPUBLIC OF SAKHA (YAKUTIA)

The article presents the results of the analysis of data from 13-year monitoring of congenital malformations (CM) in the Republic of Sakha (Yakutia) according to the Republican Genetic Register of Hereditary and Congenital Pathology of the Medical and Genetic Center of the SAI RH # 1 – NCM. The results of the application of the cartographic method in the analysis of the frequency of CM showed the geographical unevenness of its distribution on the territory of Yakutia. During the period of long-term monitoring, the highest frequency of CM was recorded in the Arctic regions of the Republic.

Keywords: congenital malformations, monitoring, medical geography, Yakutia.

Introduction. Congenital malformations (CM) are among the most serious abnormalities in children's health [4], leading to physical or mental disabilities and are the main cause of infant mortality [10, 12]. According to the World Health Organization (WHO), approximately 3.2 million children worldwide are born with CM every year, and about 300,000 newborns diagnosed with CM die within the first 28 days of life [13]. Malformations of various organ systems (cardiovascular, musculoskeletal, urinary, central nervous systems, multiple CM) make an unequal contribution to the overall indicator of the frequency of CM. The structure of malformations in the regions differs: the contribution of different organ systems to the prevalence of malformations in territorial population groups varies significantly [4].

When conducting comparative epidemiological studies of the frequency of CM in populations, it is necessary to take into account standard markers, such forms of malformations that are quite common and unambiguously diagnosed by doctors of all specialties. Long-term observation of populations by such markers makes it possible to assess the prevalence and dynamics of CM, to conduct a comparative analysis.

In many countries, CM monitoring is essentially the only effective tool for controlling the level of congenital malformations and is used to study their etiology. The main task of the monitoring system is to determine population frequencies and other epidemiological characteristics, which is of paramount importance when planning and organizing preventive measures for congenital malformations [1].

The first registers for the monitoring of CM began to work back in the 70s of the last century. Currently, two international systems of monitoring registers are successfully functioning, one of them is the European International Organization for Joint Activities in the Field of Research of Congenital Anomalies and Multiple Pregnancies (EUROCAT). EUROCAT is a joint network of 43 population registers of congenital anomalies based in 23 countries. The registries collect data on congenital anomalies that occur during live birth, late miscarriages (20-24 weeks of pregnancy), stillbirths (> 24 weeks of pregnancy) and termination of pregnancy due to fetal abnormalities [4, 9]. The second system is the International Information Center for Epidemiological Surveillance and Research in the field of birth Defects (ICBDSR), which combines surveillance programs for HPV and research projects from around the world. Currently, the organization has 42 programs from 36 countries of the world [14].

In Russia, the CM monitoring system has been operating since 1999. During all this time, the Veltischev Research and Clinical Institute for Pediatrics and Pediatric Surgery of the Pirogov Russian National Research Medical University (Department of Information Technology and Monitoring) collects and analyzes information about malformations from the regions of the Russian Federation. During this time, considerable material has been accumulated on congenital anomalies, which allows us to estimate with a high degree of reliability the frequencies of individual forms of malformations characteristic of specific regions and in total for all regions of Russia participating in monitoring [2].

In the Republic of Sakha (Yakutia), the monitoring of the CM began on the basis of the order of the Ministry of Health of 10.09.1998 No. 268 and the Order of the Ministry of Health of the RS (Ya) of 28.03.2001 No. 01-8/4-112 since 2001. A long-term study of the CM in Yakutia allowed to determine the structure, dynamics of the frequency of CM. The basic frequencies of chromosomal diseases, defects of the central nervous system and congenital heart defects by region were determined. Differences between industrial and agricultural regions of Yakutia were revealed [7]. The geographical subdivision observed in Yakutia led to further investigation of the frequency of CM by cartographic methods.

The aim of the study is a medico-geographical analysis of data on the frequency of congenital malformations in the Republic of Sakha (Yakutia).

Materials and methods. The material for the study was monitoring data from 2007 to 2020 of the Republican Genetic Register of Hereditary and Congenital

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Pathologies of the Medical Genetic Center of the SAI RH # 1 - NCM, formed on the basis of notifications of congenital malformations with updated diagnoses. The calculation of the frequency of cases of congenital malformations was carried out among 1000 births in the corresponding years of monitoring. Integral indicators of the frequency of congenital malformations for the affected body systems were calculated for the entire monitoring period with distribution over all uluses (districts) and urban districts of the Republic of Sakha (Yakutia). The frequency of congenital malformations was recorded at the place of observation of mothers.

To display the situation on the prevalence of congenital malformations among newborns in the uluses (districts) of Yakutia, a medical-geographical analysis of data on the frequency of congenital malformations among 1000 newborns was carried out using the cartographic method [3]. Malformations were grouped according to the affected body systems. The display of frequencies is carried out in five gradations of the scale of the same color: low, below average, medium, above average and high. The integral indicator of the frequency of congenital malformations for the affected organ systems is shown through a digital designation. Each digit corresponds to one of the 9 most commonly affected systems, numbered in descending order of their integral frequency. The compiled maps are aimed at the formation and extraction of spatial and territorial statistical information about the geography of the prevalence of malformations among newborns by uluses of the Republic of Sakha (Yakutia).

Results and discussion.

This study determined the frequencies of the entire spectrum of congenital malformations among newborns in the period from 2007 to 2020 in the regions of the Republic of Sakha (Yakutia). The results of the study are given in table. 1. It should be noted that during the analysis, all uluses were combined into groups - Central, Western, Arctic, Eastern and Southern [6]. These zones differ in natural and climatic conditions, levels of socio-economic development, population, ethnic composition, transport accessibility, migration processes and other parameters, which could contribute to the formation of foci of accumulation of genetic load in the population, and this, in turn, may affect the structure congenital malformations.

The results of the study showed that during the monitoring period, the weighted average frequency of the entire spectrum of congenital malformations differed from the national average, depending on the geographical and socio-economic position of the uluses. In most uluses of the Republic, with the exception of Anabarsky, Olenyoksky and Eveno-Bytantaisky, the frequency variability of the entire spectrum of congenital malformations is within the limits of statistical fluctuations, i.e. has no significant differences from the weighted average frequency for the region. At the same time, in the Anabarsky, Olenyoksky and Eveno-Bytantaysky uluses, the total frequency of congenital malformations exceeds the national average for the same period by more than 40%. This increase in frequency is statistically significant. These uluses belong to the Arctic group. As is known, the Arctic group is characterized by extreme natural and climatic and difficult socio-economic conditions, which of course negatively affects the life and general well-being of a person [5].

We also assessed the dynamics of the overall frequency of congenital malformations over the years of monitoring. During the monitoring period, two peak increases in the frequency of the entire CM

Average incidence of congenital malformations per 1000 newborns in Yakutia from 2007 to 2020

п/п	Administrative divisions	The frequency of congenital malformations per 1000 newborns
	Arctic districts	
1	Abyysky	22.19
2	Allaikhovsky	32.51
3	Anabar	48.68*
4	Bulunsky	23.15
5	Verkhnekolymsky	13.89
6	Verkhoyansky	27.95
7	Zhigansky	34.11
8	Momsky	27.70
9	Nizhnekolymsky	31.00
10	Oleneksky	40.39*
11	Srednekolymsky	23.57
12	Ust-Yansky	23.79
13	Eveno-Bytantaysky	40.43*
	Central districts	
14	Amginsky	18.14
15	Mountain	28.82
16	Kobyaysky	29.63
17	Megino-Kangalassky	19.06
18	Namsky	26.68
19	Tattinsky	31.70
20	Ust-Aldansky	37.18
21	Khangalassky	28.79
22	Churapchinsky	36.69
23	Yakutsk	37.69
	Eastern districts	
24	Oymyakonsky	28.76
25	Thompson	26.22
26	Ust-Maysky	13.38
	Western districts	
27	Verkhneviluysky	23.34
28	Vilyuysky	24.88
29	Lensky	10.47
30	Mirninsky	11.77
31	Nyurbinsky	34.91
32	Suntarsky	31.34
	Southern districts	
33	Aldansky	14.99
34	Neryungrinsky	14.27
35	Olekminsky	17.28
	Average for Yakutia	
36	Republic of Sakha (Yakutia)	28.47*

Note: * - statistically significant differences.

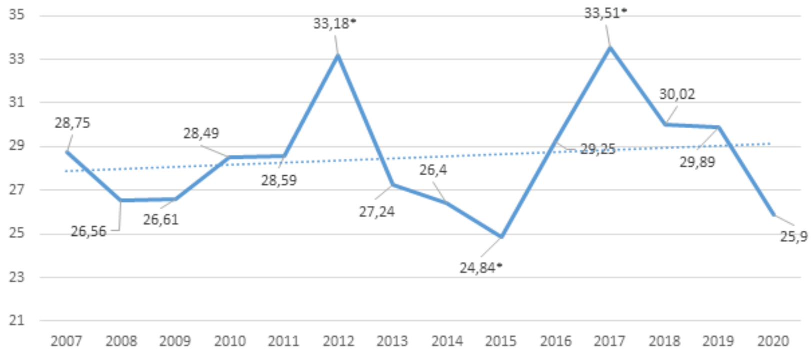

Fig. 1 - Dynamics of the overall incidence of congenital malformations per 1000 newborns 2007-2020

Note: *- statistically significant indicators

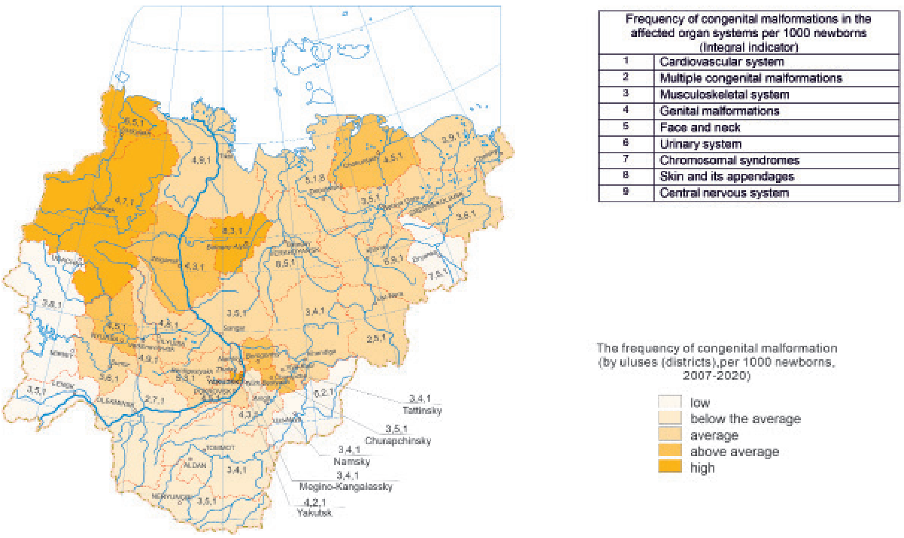

Fig. 2. The frequency of congenital malformations (by uluses (district), per 1000 newborns, 2007-2020)

spectrum were observed - in 2012 and 2017. During these years, the frequency of CM was statistically significantly higher than the weighted average frequency in Yakutia for the entire monitoring period. At the same time, in 2015 there was a significant decrease in this indicator. The dynamics of the CM frequency is illustrated in Fig.1.

Further, a medical-geographical study was carried out, the results of which are shown in Fig.2. This analysis clearly demonstrated the uneven geographical distribution of the overall frequency of congenital malformations and affected body systems. High rates of the overall frequency of congenital malformations were noted in the Arctic and Central uluses of Yakutia. The cardiovascular and musculoskeletal systems are most often affected, and multiple lesions of different systems are often recorded. A low frequency of malformations is recorded in the Western and Southern groups of uluses. At the same time, it is considered that the overall frequency of congenital malformations should be above 20 cases per 1000 births. Lower rates may be the result of insufficient detection or registration of malformations [11]. It should be emphasized that the Southern group of uluses is characterized by a low birth rate [8].

Since 2012, the republic has been implementing a program for early prenatal diagnosis of CM and chromosomal abnormalities, according to the decision of the perinatal council, the level of medical care and routing of pregnant women are determined depending on the severity of congenital malformations. At the same time, in cases of severe and uncorrectable CM, a decision is made to eliminate the fetus. The frequency of registration and the nature of CM can also be an indicator of the level and quality of prenatal diagnostics in each of the 35 administrative units of Yakutia.

Conclusion.

According to the monitoring data, the observed features of the distribution of the frequency of CM may be due to different birth rates and diagnostic capabilities of medical organizations in Yakutia. The geographical factor (remoteness, inaccessibility of territories) can still influence the formation of the population frequency of congenital malformations among certain groups of the population of the North. During the study period, there is a wave-like frequency dynamics of the entire CM spectrum with intervals of 2-3 years between peak values. This pattern may be explained by some intra-population processes that have not been studied in this work. According to the results of monitoring for 2007-2020, the weighted average frequency of congenital malformations in the Republic of Sakha (Yakutia) was 28.47 cases per 1000 newborns. Despite the significant dynamics of the overall frequency of CM in some years, there was no stable tendency to decrease or increase this indicator. The problem of high frequency of CM persists in the Arctic group of Yakutia uluses. Thus, in the Eveno-Bytantay and Olenek uluses, the total frequency of compulsory registration CM during the monitoring period exceeds the national average by 1.5-2 times.

The data obtained will make it possible to take measures to improve the organization of monitoring, periconceptional prevention and prenatal diagnosis of CM in the republic.

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ARCTIC MEDICINE

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ASSOCIATION OF GENE POLYMORPHISM *PTGS2* rs689466 WITH PLASMA IRISIN LEVEL IN YAKUTS

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Prostaglandin E2 may be involved in an increase in body temperature during cold stress by the type of fever. At the same time, a significant part of heat production is produced during shivering thermogenesis, due to arbitrary muscle activity, which is accompanied by the release of the hormone irisin. Prostaglandin E2 is formed from arachidonic acid by the enzyme cyclooxygenase-2, which is encoded by the *PTGS2* gene. The transcriptional activity of the *PTGS2* gene depends on its allelic variants, which can affect thermoregulation processes in different ways. In this regard, the aim of this study is to analyze the polymorphism rs689466 of the *PTGS2* gene with the level of irisin in blood plasma in a population of Yakuts living in cold climatic conditions. The study involved 183 women and 80 men (average age 19.73±1.99 years). Analysis of the association of polymorphism rs689466 of the *PTGS2* gene with irisin levels showed that in men with the TT genotype, irisin levels (8.2±1.85 μg/ml) were statistically significantly higher (U=261; p=0.005), compared with men with CT+CC genotypes (7.1±1.25 μg/ml). In addition, it was found that men with the TT genotype (63.6±6.67 kg) had a lower weight than men with the CT+CC genotypes (67.93±7.28 kg; U=279; p=0.01). The detected association of the TT rs689466 genotype of the *PTGS2* gene with elevated irisin levels and with a lower weight in men may indicate the effect of prostaglandin E2 on shivering thermogenesis during cold stress, which may play a role in human adaptation to a cold climate.

Keywords: irisin, prostaglandin E2, gene *PTGS2*, rs689466, fever, cold stress.

Introduction. One of the key mechanisms in human physiology is the ability to sense and regulate body temperature, which is crucial for survival. The body's defense reactions include fever, which is accompanied by an increase in body temperature in response to pyrogens [14] that stimulates an immune response [6]. An increase in body temperature during fever occurs due to shivering (in skeletal muscles) and nonshivering (in brown adipose tissue) thermogenesis, and a decrease in passive heat loss occurs due to vasoconstriction [8]. However, the main contribution to increased heat production in fever is made by shivering thermogenesis, which is accompanied by involuntary muscle contraction (shiver) and the release of the hormone irisin into the blood [7,15].

Prostaglandin E2 is a principal fever mediator that can also control the basal mechanisms of thermoregulation. In 2015, J. Foster and his colleagues pub-