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SCIENTIFIC REVIEWS AND LECTURES

R.N. Mustafin, A.V. Kazantseva, E.K. Khusnutdinova

THE ROLE OF COVID-19 IN MODIFIED COGNITIVE FUNCTIONING

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SARS-CoV-2 virus impairs cognitive functions during illness and in long-term periods: from 3 months (in 44% of patients) to one year (in 16.2% - 63% of patients) after recovery. Cognitive deficits are more common in patients with severe COVID-19, especially those treated in the intensive care unit, and with infection duration of more than 28 days. Such consequences are associated with direct impact of SARS-CoV-2 on the functioning of brain neurons and changes mediated by endothelial dysfunction due to impaired blood supply to the cerebral cortex. The long-term results of the viral effect on brain neurons are due to immune responses to the virus multiplying in cells and to changes in the epigenetic regulation of gene expression. The immune response leads to inflammation, which is expressed in the form of encephalitis, encephalopathy, anosmia, hypogeusia and is reflected in the development of cognitive deficit. Epigenetic changes are mediated by virus-induced activation of retroelements that have cis- and trans-effects on genes involved in neurogenesis. SARS-CoV-2 promotes the expression of miRNAs that silence the expression of many genes, thus impairing cognitive functioning. The mechanism of these changes is associated with the effect of the virus on retroelements, which are the sources of miRNAs. Reverse transcriptase and endonuclease of retroelements may be involved in the integration of SARS-CoV-2 into the human genome, which may also affect the change in the expression of genes necessary for cognitive development.

Keywords: cognitive functions; microRNA; retroelements; COVID-19.

Introduction. The COVID-19 pandemic remains an urgent problem for all mankind both due to a high mortality rate and due to the consequences, which are developed after recovery. Since individual cognitive functions (CF) inherently determine the ability of complete functioning, professional skills and self-care, the question on the impact of COVID-19 on cognitive functioning remains relevant. Indeed, it is impossible to imagine individual's life without CF [24, 35], that can be adversely affected by the virus. Back in 2020, the analysis of 214 hospitalized patients with COVID-19 in Wuhan, China, showed the development of neurological impairments in 41.1% of patients [34]. Modified cognitive functioning in patients after recovery remains highly relevant [47]. COVID-19 also accelerates neurodegenerative processes in the elderly [2].

The most pronounced cognitive impairments are detected in severe patients who require intensive care (IT) during hospitalization [21]. Thus, the study of 92 COVID-19 patients, who required IT therapy, were characterized by pathological cognitive changes in 44% of cases 3 months after recovery [47]. The duration of infection plays an important role. In the study of 3,762 patients from 56 countries with a confirmed diagnosis of COVID-19, which duration was more than 28 days, cognitive dysfunction and memory problems were identified in all age groups in 88% of patients [11]. Nevertheless, another study of 81,337 patients after COVID-19 recovery demonstrated that cognitive deficit developed even in individuals with asymptomatic course of the disease compared with the control group [19].

Indicators of the frequency of cognitive impairments observed after COVID-19 recovery differ in the studies from various countries. However, significantly en-

MUSTAFIN Rustam Nailevich – PhD, associate professor, Bashkir State Medical University, ruji79@mail.ru; **KAZANTSEVA Anastasiya Valerievna –** PhD in Biology, senior researcher, Institute of Biochemictry and Genetics, Subdivision of the Ufa Federal Research Centre of the Russian Academy of Sciences, ORCID: 0000-0002-3744-8058; **KHUSNUTDINOVA Elza Kamilevna –** Doctor in Biology, Professor, corresponding member, Director of the Institute of Biochemistry and Genetics UFRC RAS, head of the department UUST, ORCID ID: 0000-0003-2987-3334.

hanced frequency of cognitive changes in infected patients compared to control groups was characteristic for all of them. Longitudinal studies of cognitive functions in 452 patients in the Netherlands indicate the development of psychiatric symptoms in 26.2% and cognitive decline in 16.2% of individuals one year after IT for COVID-19 treatment [21]. In Spain, the assessment of cognitive functions carried out one year after COVID-19 hospitalization revealed the presence of neurocognitive dysfunction in 46.8% and mental illness in 45% of cases [38]. In Italy, cognitive deficits were detected in 13.5% of patients 4 months after IT for COVID-19 treatment and only in 1.2% of patients with mild to moderate illness without hospitalization [36]. The study of 92 COVID-19 patients in Mexico reported the presence of cognitive impairments in 54.4% of patients after 6 months [16]. In the USA, the analysis of cognitive changes conducted in 156 patients revealed at least mild cognitive impairment according to Neuro-Qol in 63% of patients 351 days after COVID-19 recovery [52]. These long-term effects are due to the direct and indirect effects of the virus on brain neurons.

Direct effect of SARS-CoV-2 on cognitive functioning. A direct effect of SARS-CoV-2 on the central nervous system was evidenced in empirical research, which demonstarted that neuronal stem cells (NSCs) were sensitive to the penetration of the virus. Extensive expression of infectious SARS-CoV-2 particles and their proteins was detected in the neurospheres and brain organoids including the cerebral cortex and NSC [56]. It was proved that the virus penetrated into the central nervous system through the olfactory mucosa, and subsequently via thin olfactory sensitive nerve fibers into the brain. The SARS-CoV-2 virus has a tropism to neurons and is distributed to certain neuroanatomic regions, including the respiratory and cardiovascular centers in the medulla oblongata, where it actively multiplies and indirectly causes vascular damage. Morphological post-mortem examination of COVID-19 individuals showed the presence of foci of acute ischemic strokes due to thromboembolism, which regions were characterize by increased levels of immune reactivity to S protein of the SARS-Cov-2 [37]. SARS-CoV-2 induces inflammatory processes in CNS regions responsible for memory, learning and emotional responses due to damage to neurotransmission and neurogenesis [27].

The immune response to the multiplying virus in neurons causes inflammatory reactions in the brain, which is reflected by the development of specific clinical manifestations. The retrospective multicenter analysis of 232 COVID-19 patients in Spain reported that the onset of neurological symptoms, on average, was determined on the 8th day from the infection onset. The development of encephalopathy or encephalitis was observed in 21.9% of the examined patients, while 7.8% had brain lesions diagnosed with MRI and 61.9% - with EEG [1]. Meta-analysis conducted on 3,868 patients confirmed the development of delirium in 27% of COVID-19 patients [45]. A possible consequence of a direct effect of SARS-CoV-2 on cognitive functioning is anosmia detected in 44% of infected patients and hypogeusia (decreased taste sense) - in 43% [9]. The study of 514,459 patients with a positive test for SARS-CoV-2 examined using 6 National digital surveillance platforms revealed the presence of anosmia/ageusia in 43% of COVID-19 patients in the USA, 29% - in the UK, and 14% - in Israel, which was significantly higher compared to individuals with negative PCR tests [51]. A direct effect of SARS-CoV-2 on CNS neurons with a violation of the blood-brain barrier can be confirmed by the detected viral antigens in the cerebrospinal fluid (CSF) of COVID-19 patients [3]. In experiments with mice infected with SARS-CoV-2, a selective microglial reactivation of the white matter of the brain was revealed. Similar changes have been identified in the post-mortem brain tissues of COVID-19 patients. Within 7 weeks after murine infection, an enhanced level of proinflammatory cytokines/chemokines. It was accompanied by suppression of neurogenesis in the hippocampus, a decreased number of oligodendrocytes and loss of myelin in the subcortical white matter [14].

Indirect effect of COVID-19 on cognitive impairment. Impaired cognitive functioning during infection and in the long-term periods after recovery may be due to hypoxia caused by damage of lung tissue. This is evidenced by data on more frequent occurrence of cognitive deficits in severe COVID-19 patients [21, 47], and in those with prolonged course of the disease [11], since they are accompanied by intense oxygen starvation of the brain [16]. The situation is aggravated by concomitant damage of the CNS due to inflammation and endothelial dysfunction. The study based on 749 COVID-19 patients demonstrated an impaired signal intensity in MRI of the cerebral cortex in 37% of patients with neurological symptoms [23]. Long-term impairments (after 6 months) of cognitive functions have been directly related to the level of hypoxemia during COVID-19 [16].

A cause of neurological diseases may be atherosclerosis and endothelial cells (EC) dysfunction. A flow–mediated dilation (FMD) represents one of the indicators of a dysfunction. Impaired FMD is observed with worsened cognitive functioning, especially with respect to attention, executive functions, and memory. Recovering COVID-19 patients are characterized by endothelial dysfunction with a direct correlation between the severity of lung and vascular lesions, which may play an important role in modified cognitive functioning in patient [39]. A retrospective analysis of global data on the COVID-19 consequences demonstrated the development of ischemic stroke in 1.3% of 8,163 infected individuals compared with 1% among 19,513 patients without COVID-19. This indicates a slight but significant increase in the risk of stroke caused by SARS-CoV-2 [46]. The study of 21,483 COVID-19 adult patients, who took a therapy in 107 hospitals in the USA, 0.2% of them reported spontaneous intracranial hemorrhages [30].

Endothelial dysfunction is caused by a direct effect of SARS-CoV-2 on EC, which abundantly express angiotensin-converting enzyme 2 (ACE2). The ACE2 protein is a receptor for the virus, facilitating its penetration into the cells and resulting in the activation of immune response that causes a cascade of coagulation and subsequent vasculopathy [8]. Impaired EC and coagulopathy are related to the inflammatory processes in the brain, as evidenced by the detection of antibodies against SARS-CoV-2 in the CSF of COVID-19 patients [3] in 77% of the studied cases [15]. Activated macrophages, which initiate inflammation through the TLR4-MyD88 signaling pathways, are detected in the brain of patients. As a result, high levels of IL-6, IL-18, CC-chemokine ligand 2 (CCL2), and a soluble cell adhesion molecule (sICAM-1) are detected in CSF of patients [37]. The most expressed increase in proinflammatory cytokines IL-6, IL-10, ferritin and D-dimer in CSF was determined in COVID-19 patients with strokes, which is comparable to similar indicators in post-stroke patients without COVID-19 [15].

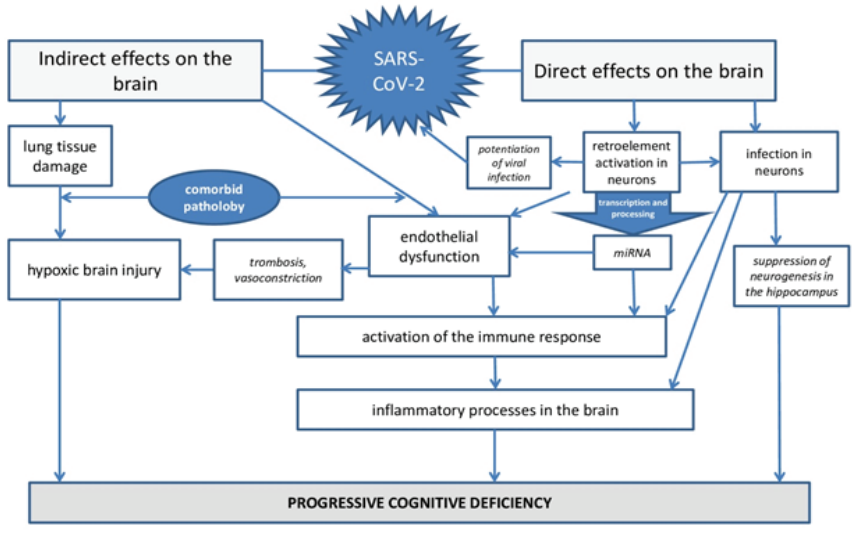
The impact of COVID-19 on CF related to EC dysfunction with long-term consequences can be compare with the progressive dementia in aging population, an important role in it is played by microRNAs such as miR-128, miR-132, miR-134, miR-222, miR-323-3p, miR-382, miR-409-3p, miR-451a, miR-486-5p,

miR-502-3p, and miR-874 [57]. Dynamic changes in microRNA levels regulate the expression of genes involved in CF such as learning and memory [41, 55]. The microRNAs affecting the genes responsible for brain functioning are involved in the pathogenesis of vascular dementia. Thus, the target for miR-124 (inhibits the formation of Aß) is the *BACE1* gene; miR-126 (improves vascular function) – the *MMP-9* gene; miR-132 (protects against chronic cerebral hypoperfusion) – the *Nav1.1,* and *Nav1.2*genes; miR-134-5p (promotes damage to cortical neurons) – the *Snap25* gene; miR-195 – the *APP, BACE1* genes; miR-153 (contributes to the abnormal synaptic plasticity) – the *Snap25, Vamp2, Stx1a,* and *Syt1* genes; miR-181c (enhances cellular adaptation during prolonged ischemia), miR-210-5p (reduces the number of synapses) – the *Snap25* gene; miR-26b (suppresses the inflammatory reaction of microglia) – the *IL6* gene; miR-501-3p (aggravates damage of the blood-brain barrier) – the *ZO-1* gene; miR-9 (induces impaired cognitive functioning) – the *Nav1.1, Nav1.2, BACE1* genes; miR-93 (enhances inflammatory reactions) – the *TLR* gene; miR-96 (inhibits autophagy) – the *mTOR* gene [57]. The most studied microRNAs associated with cognitive functions is the cluster of miR-132/212, which are actively expressed in neurons and localized in synaptodendritic fractions. Their hippocampal levels are significantly increased as a result of cognitive training. The miR-134 suppresses the formation of dendrite spikes due to *Limk1, Creb and Bdnf* silencing. In addition, miR-34a negatively affects dendrites growth and branching, weakening a synaptic plasticity of neurons. The levels of miR-34a and miR-128b in the basolateral amygdala are increased with fear, while miR-34a suppression by microRNA sponges reduces fear memory [55]. The microRNAs miR-140-5p, miR-197-3p and miR-501-3p can be used as biomarkers of cognitive aging [18]. It can be assumed that miRNAs play a role in the development of cognitive disorders in patients after COVID-19 due to the activation of retroelements (REs) caused by SARS-CoV-2, since REs are the most important sources of human microRNAs [31, 54].

The role of retroelements in developing COVID-19 cognitive consequences. A direct effect of SARS-CoV-2 on impaired cognitive functioning is caused by both a direct infectious process in neurons and immune-inflammatory reactions, and the impact on the expression of specific genes involved in CF. It is assumed that this observation is attributed to the activation of mobile genetic elements (TE – transposable elements), which are divided into DNA transposons and REs according to the mechanism of their translocation in the genome. More than 40% of the human genome consists of REs, including 8% are endogenous retroviruses (ERV), which contain LTR (long terminal repeats) [42]. About 33% of human genome consists of non-LTR-containing REs: autonomous LINE1 (L1) and non-autonomous SINE [29]. In the evolution of primates, several LINE retrotranspositions and the formation of novel REs related to SINE and SVA (SINE/VNTR/Alu) occurred, which significantly affected brain development [32]. This process can explain a pronounced activity of L1 in the regions of neurogenesis in the human hippocampus. Somatic transpositions of L1 have a programmed effect on the expression of specific neuronal genes, thus forming unique transcriptomes of individual neurons for the development of cognitive abilities [40]. Therefore, somatic retrotranspositions of L1 are the sources of genetic mosaicism and potential phenotypic diversity of neurons in brain development. The expression of L1 in adults may be due to various environmental influences, affecting neuronal stem cells differentiation. Murine experiments demonstrated the role of L1 expression in the formation of long-term memory, which indicates the importance of REs in cognitive functioning [5]. COVID-19 causes a significant impairment in neurogenesis in the hippocampus [27], which may be attributed to a pathological activation of RE due to the viral exposure [5].

The most common SINE elements in the human genome are Alu (comprise about 11% of all DNA), which require L1 enzymes for their own transpositions. It is assumed that Alu contributed to the formation of cognitive functions in humans, since they play a crucial role in the development of connections between the neurons and in epigenetic regulation of biochemical processes in the brain. However, the involvement of REs in the management of gene expression in the CNS is a subtle and evolutionarily programmed species-specific process. In this regard, specific deviations from it due to pathological activation of REs and nonspecific transposition can cause serious consequences. Thus, non-programmed Alu translocations have been described as the causes of a large number of neurodegenerative diseases [29]. In murine experiments, ERV activation in the CNS resulted in hippocampal-related memory impairment and cognitive deficits [48].

Within the evolution, REs were the sources of various protein-encoding genes (molecular domestication). A comparative genomic and functional analysis has shown the origin of many human genes from ERVs. These genes are involved in development of placenta and immune responses, and in the regulation of cognitive functioning. They include the *Zcchc16, Arc, Mart4,* and *Sirh11* [42]. REs affect cognitive development in several ways. Firstly, the programmed somatic activation of REs in neuronal stem cells determines the specificity of differentiation and subsequent functioning of mature cells. Secondly, genes, which originated from Res in the evolution, are involved in regulatory pathways controlled by various REs. In this regard, pathological activation of REs due to exposure to SARS-CoV-2, can result in



The scheme of mechanisms of COVID-19 effect on modified cognitive functioning

cognitive changes. In particular, in mice, the *Sirh11/Zcchc16* (11/Zinc finger CCHC domain-containing 16) gene, which is a homologueof Sushi-ichi-related RE, is responsible for regulation of cognitive functions including attention, impulsivity and working memory [22].

The Arc protein (encoded by the *IEG* gene – immediate-early gene), which mRNA is specifically located in the synaptic region, thus regulating synaptic plasticity and memory formation, also occurred in evolution through the "domestication" of RE genes [10]. Enhanced Arc expression in hippocampal neurons *in vitro* was shown to increase the number of dendrite spikes, while suppression of Arc synthesis *in vivo* reduced the density of hippocampal neuronal spikes in mice [43]. This protein is required for spatial learning, object recognition, contextual tasks for inhibited avoidance, taste aversion, fear formation, memory reconsolidation, reactions to visual experience and deprivation, network excitability, Alzheimer's and Angelman's diseases, fragile X chromosome syndrome [28]. In addition, a reduced Arc transcription was observed in the neurogenesis region in the hippocampus during aging (in rat models) [44]. The role of mutations in the Arc-encoding gene in the development of autism and schizophrenia has been described. At the same time, an inducing influence of exogenous viral infections could not be excluded, since Arc preserves the properties of exogenous viruses, which are used for information transfer between the neurons and innervated organs. In particular, experiments with drosophila revealed that Arc forms structures similar to the viral capsid, which pack mRNA in the neurons of the brain. Formed structures are loaded into extracellular vesicles, which are transmitted from the motor neurons to the muscles. 3'-untranslated region of the gene contains RE-like sequences required for the loading of capsid structures into vesicles [4]. The mammalian *PEG10* gene, homologous to ERV *gag*, has similar properties. Its encoded protein binds to its mRNA for its secretion into vesicles [49].

Viruses modulate the activity of REs, which affects the expression of the downstream genes of the hosts. The analysis of ChiP-Seq data revealed a differential expression of REs located in the transcription factors binding sites, which regulate the expression of genes involved in the immune response in COVID-19. Enhanced levels of 52 HERV and 40 LINE1 was detected on cell lines infected with SARS-CoV-2 [35]. Since HERVs can be activated in response to infectious agents, causing the development of various immune pathological effects, the analysis of HERV changes in 17 COVID-19 patients was performed. HERV-W was highly expressed in patients infected with SARS-CoV-2 compared to healthy controls. HERV-W levels correlated with the markers of T-lymphocyte differentiation and cytokine levels in the blood (IL-6, IL-17, TNF-α, CCL-2, and CXCL6). The percentage of HERV-W ENV-positive lymphocytes correlated with inflammatory markers and severity of pneumonia in COVID-19 patients, as well as with poor outcomes of hospitalized patients [6]. *In vitro* study demonstrated an increased expression of the HERV-W envelope protein as a result of the introduction of the SARS-CoV-2 spike protein into the leukocyte culture [17]. Comparative analysis of the transcriptome of bronchoalveolar lavage and peripheral blood monocytes of COVID-19 patients and healthy subjects indicated a significant increase in the levels of HERV transcripts in bronchoalveolar fluid in SARS-CoV-2 infected individuals, to a greater extent in elderly [26]. The study of children with COVID-19 revealed a positive correlation between the expression of HERV and *IFN-I, IFN-II, TRIM28, SETDB1* genes, which products are involved in immune responses to the virus [53].

Together with the effect of SARS-CoV-2 on the changes in the expression of REs, it is assumed that the TEs themselves play an important role in modulating COVID-19 infection, since HERVs are involved in the regulation of the immune system and can participate in the mechanisms of infection and viral penetration into the cells. In addition, HERV synthesizes proteins that complement the viral set of ORFs during penetration, infection, replication, packaging and integration of SARS-CoV-2 into the human genome. The products of HERV expression can also modulate the initiation of translation on the ribosome by changing ORFs pattern of SARS-CoV-2 in different cells, which affects the severity of infection [12]. REs can mediate EC dysfunction in COVID-19, since translocation of activated L1 into the novel genomic loci results in reduced proliferation and migration of EC via selective influence on such angiogenic factors as Tie-2 (protein kinase receptor) and VEGF [7].

The phenomenon of long-term detection of SARS-CoV-2 RNA in patients after COVID-19 recovery, made it possible to suggest the integration of viral cDNA into the host genome, which was confirmed on human cell cultures. Duplications of the target site flanking the viral sequence were found together with consensus sequences of recognition by endonuclease L1 in integration sites. The data obtained indicate the mechanism of reverse transcription and retroposition of SARS-CoV-2 via L1. An additional confirmation was the data on the detection of viral sequences in the tissues of COVID-19 patients, which transcribed from integrated DNA copies of SARS-CoV-2, creating chimeric transcripts of the virus and the host [58]. Thus, the role of REs in COVID-19-caused cognitive decline is related to the possible activation of Res by SARS-CoV-2, which aggravate the clinical course of the disease by changing the expression of specific genes responsible for cognitive functioning. Moreover, individual specificty of HERV affect the COVID-19 course by modulating the immune response and viral transcription, while RE-encoded proteins can participate in the integration of SARS-CoV-2 into the human genome, which affects the long-term consequences of infection including the deterioration of brain functioning.

Conclusion. SARS-CoV-2 causes cognitive impairment both by direct impact of the virus on brain neurons and by endothelial dysfunction (Fig. 1). The study of the mechanisms of COVID-19 influence on modified cognitive functioning can become the basis for effective therapy of impaired functioning. Interactive cognitive-motor training can be one of the ways [2]. It is also proposed to use REs and evolutionary derived genes, such as *PEG10*, capable to form virus-like particles exported to extracellular vesicles, for targeted therapy of cognitive impairment caused by exposure to SARS-CoV-2 [49]. This approach is especially relevant due to the role of REs as effectors of changed viral-related brain functioning, and the important role of REs as microRNAs sources [31, 54]. The latter, like the products of *PEG10* [49] and *IEG* [4] genes expression, are exported into extracellular vesicles from neurons. The results of clinical studies of elderly individuals over 65 years indicated that reduced stress could improve cognitive functioning by increasing miR-29 expression (with its immersion in vesicles) and suppressing the production of DNA methyltransferases DNMT3A/3B in neurons [20]. The analysis of the role of specific microRNAs in restoration of cognitive functions can become the basis for both targeted therapy and predicting the significance of certain approaches in patients' therapy. In particular, a favorable role of physical exercises in improved cognitive functioning was reported via

modulating the expression of miR-146a, miR-21, miR-223 in humans [13]. Restoration of CF is proposed to be performed with miR-218, which regulates contextual and spatial memory due to the activating effect on the complement component C3 gene necessary for presynaptic cognitive functioning in the hippocampus [33]. REs and microRNAs can be used to develop novel approaches for COVID-19 treatment. Information analysis revealed 21 human microRNAs homologous to the SARS-CoV-2 genome and capable of inhibition of transmission and replication of viral RNAs. Of these, the most effective were miR-1296, miR-3202, miR-4476, miR-548-1d, miR-651 [50].

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T.M. Sivtseva, T.M. Klimova, R.N. Zakharova, E.P. Ammosova, V.L. Osakovsky

THE ROLE OF *FADS* GENE POLYMORPHIC VARIANTS IN ADAPTATION TO THE NORTHERN CLIMATE AND METABOLIC DISORDERS

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SIVTSEVA Tatiana Mikhailovna – PhD, leading researcher, Research Center of the Medical institute, M.K. Ammosov North-Eastern Federal University: sivtceva@list.ru, ORCID 0000-0002-1501-7433; **KLIMOVA Tatiana Mikhailovna** – PhD, Associate Professor, senior researcher of the Department of Pharmacology and Pharmacy, Senior Researcher of the Research Center of the Medical Institute of the M.K. Ammosov North-Eastern Federal University, Senior Researcher, Department of Epidemiology of Chronic Diseases, Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia, ORCID: 0000-0003-2746-0608; **ZAKHAROVA Raisa Nikolaevna** – Ph.D., leading researcher, Research Center of the Medical Institute of the M.K. Ammosov North-Eastern Federal University, ORCID: 0000-0002-1395-8256; **OSAKOVSKY Vladimir Leonidovich** – Ph.D., chief researcher, Research Center of the Medical Institute of the M.K. Ammosov North-Eastern Federal University, ORCID 0000-0001-9529-2488; **AMMOSOVA Elena Petrovna** – Ph.D., leading researcher, Research Center of the Medical Institute of the M.K. Ammosov North-Eastern Federal University, doctor of Functional Diagnostics of the State Autonomous Institution of the Republic of Sakha (Yakutia) Yakutsk City Hospital No. 3, e-mail: ammosovael@mail.ru. ORCID: 0000-0002-7973-6103.

The review summarizes the studies of the role of the *FADS* gene in the metabolism of polyunsaturated fatty acids, as one of the mechanisms of human adaptation to the environmental conditions, in particular, a cold climate. A comparative analysis of the distribution of the most significant for circumpolar ethnic groups polymorphic variants rs7115739, rs174570 of the *FADS* 2-3 genes in various ethnic groups, including the Inuits and Yakuts, was carried out. The results of studies of the *FADS* polymorphic markers effect on lipid metabolism, the risk of cardiovascular diseases and type 2 diabetes mellitus in different world populations are systematized.

Keywords: *FADS* genes, desaturases, polyunsaturated fatty acids, rs7115739, rs174570, metabolism, adaptation, cold, North, Yakuts.

Introduction. Currently, the contribution of *FADS* cluster genes associated with the synthesis of long-chain polyunsaturated fatty acids (LC-PUFAs) in the development of metabolic disorders, increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (DM2) is being actively studied. LC-PUFAs are involved in many physiological processes: they are part of cell membranes, serve as a substrate for the synthesis of inflammatory eicosanoids (leukotrienes and prostaglandins), act as signaling molecules, and regulate gene expression [42]. One of the main LC-PUFAs are eicosapentaenoic (EPA), docosahexaenoic (DHA) and arachidonic (AA) acids, the last two are necessary for the full functioning of the central nervous system [43]. These fatty acids are not synthesized in the body *de novo*, therefore, they must be supplied with food, or in the form of their 18-carbon substrates for endogenous biosynthesis (omega-6 linoleic (LA) and omega-3 alpha-linolenic acids (ALA)) [42]. The content of LC-PUFAs and their precursors in the traditional diet of various world populations varies greatly depending on the geography and type of economic activity. EPA and DHA,