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# THE ROLE OF THE BDNF (RS6265) AND CNTF (RS1800169) GENE POLYMORPHIC VARIANTS IN THE DEVELOPMENT AND PROGRESSION OF NEUROLOGICAL DISORDERS

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In recent decades the contribution of polymorphic variants of genes encoding neuroinflammation and neuroprotection proteins in pathology of the nervous system has been actively studied. Numerous studies have demonstrated the most important structural and functional role of single nucleotide variants in the BDNF and CNTF genes in the brain. This review provides evidence of the association of polymorphic loci of the BDNF and CNTF genes with a number of neurological disorders. It was found that an increased risk of developing depressive disorders, Alzheimer's and Parkinson's diseases are characteristic of the BDNF rs6265 polymorphism carriers. Moreover, the above mutation affects the length of stay in rehabilitation and the duration of remission in patients with substance dependence. A number of authors provide contradictory information about the relationship of the BDNF rs6265 genetic variant with changes in neurotrophin levels in schizophrenia. The BDNF rs6265 A/A genotype carriers in Caucasian and Asian populations showed an increased risk of the disease. The CNTF rs1800169 genetic variant does not affect the risk of schizophrenia in general but may play a more prominent role in its clinical manifestations together with other CNTF gene mutations. Some studies have shown an association of the rs1800169 polymorphism in the CNTF gene with schizophrenia spectrum disorders. A number of studies have confirmed a negative association between the rs1800169 polymorphism in the CNTF gene and Alzheimer's disease. Further studies are needed to clarify the role of the BDNF and CNTF genetic variants in pathology of the nervous system and to find an effective treatment.

**Keywords:** brain-derived neurotrophic factor, ciliary neurotrophic factor, the BDNF gene, the CNTF gene, SNP markers, genetic predisposition, neurological disorders.

**Introduction.** Nowadays neurological disorders remain one of the leading causes of disability and premature death and contribute significantly to the global burden of disease [5]. The development of molecular genetic methods has led to an increasing number of association studies of polymorphic variants of genes encoding proteins of neuroinflammation and neuroprotection which include brain-derived neurotrophic factor and ciliary neurotrophic factor.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and expressed in the central and peripheral nervous system, vascular endothelium, leukocytes, platelets, megakaryocytes, and muscles. Its functions are carried out through signaling pathways activated by TrkB (tropomyosin receptor kinase B) and p75NTR (p75 neurotrophin receptor) receptors. BDNF is found to be essential for the proper functioning of the nervous system and implicated in the pathogenesis of neural diseases. This neurotrophin modulates the work of dopaminergic neurons, myelination of nerve fibers, stimulates axon growth, synaptogenesis, and participates in the regulation of neuroplastic processes (long-term potentialization and depression of synaptic transmission). In the developing nervous system it promotes synaptic pruning, and also performs a neuroprotective function when being exposed to damaging factors. In addition, BDNF participates in the processes of oncogenesis, angiogenesis, gluconeogenesis and others [3, 25].

Ciliary neurotrophic factor (CNTF) belongs to the cytokines of the interleukin-6 family and performs a number of functions by binding to the high-affinity receptor complex CNTFRα/GP130/LIFRβ (CNTF receptor α/glycoprotein 130 receptor β/leukemia inhibitor factor receptor β). This cytokine supports self-renewal and differentiation of neural stem cells, stimulates neurite growth in sensory neurons, inhibits apoptosis of spinal ganglion neurons, accelerates regeneration of motor neurons and skeletal muscles, and participates in mechanisms of cardioprotection. CNTF plays an important role in the pathogenesis and treatment of psychiatric disorders, affective behavior, neurodegenerative diseases, spinal cord injury, and retinal degeneration. In addition, it is essential for energy metabolism: it activates in the hypothalamus pathogenetic pathways related to leptin metabolism. CNTF expression has been confirmed in astrocytes, Schwann cells, retinal pigment epithelium, and Müller cells [12].

**The aim** of this review is to update, systematize and summarize the data of scientific publications on the role of single nucleotide variants of the BDNF and CNTF genes in the pathogenesis of neurological disorders. To achieve this goal we have searched for English and Russian articles (up to 2023 inclusive) in Pubmed, Google Scholar, and eLibrary databases and have used the descriptive method.

**The rs6265 polymorphism of the BDNF gene.** The human BDNF gene is located on the short arm of chromosome 11 (locus 11p14.1) and includes

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12 exons. Recently more than 25000 of its polymorphic variants have been described, the most studied among them is the rs6265 polymorphism, associated with an increased risk of nervous system pathologies [4]. Transition of G to A in position 196 leads to the replacement of valine by methionine in codon 66. As a result of the mutation in the pro-domain, transport and secretion of neurotrophin are impaired [33]. Correlations between the rs6265 polymorphism of the BDNF gene, morphological changes in the brain and the results of cognitive tests have been found. Carriers of the BDNF rs6265 minor allele showed a decrease in the thickness of the hippocampal cortex, frontal lobe, caudate nucleus and amygdala, as well as in the volume of gray matter of the prefrontal cortex and hippocampus. This polymorphism is associated with decreased synaptic plasticity (mainly long-term potentialization and depression), impaired regulation of the hypothalamic-pituitary-adrenal system, worse working, episodic, spatial memory, executive functions, information processing speed, motor learning ability, and task performance [4, 31]. The frequency of the BDNF rs6265 A allele in the Russian population (14.5%) correlates with the distribution of similar data in European (19.4%) and Latin American (14.8%) countries [20].

M. Svetel et al. showed that the presence of the minor allele of the rs6265 locus of the BDNF gene did not affect the clinical characteristics of patients with Parkinson's disease (sex, family history, age of onset, severity of the disease course, cognitive function, severity of motor symptoms) [38], but contributed to an increase in the number of non-motor disorders [6]. Carriers of the BDNF rs6265 minor allele had worse scores on the United Parkinson's Disease Rating Scale (UPDRS) during levodopa monotherapy compared to those with the G/G genotype carriers [7]. Moreover, patients expressing the A allele of the rs6265 locus of the BDNF gene have a higher risk of developing levodopa-induced dyskinesia in early treatment compared to G/G genotype carriers [8]. Identification of genetic variants, such as the rs6265 polymorphism, allows predicting the nature of the disease and selecting effective treatment methods.

H. Ji et al. found no statistically significant relationship between the rs6265 polymorphism of the BDNF gene and Alzheimer's disease, but its prevalence is slightly varied in different populations [14]. It has been shown that the risk of developing the disease is higher in female with A allele of this gene, and predominantly in Caucasian women [27]. Patients with the BDNF rs6265 minor allele and dominantly inherited form of the disease associated with mutations of the APP, PSEN1, PSEN2 genes showed faster memory decline (4x), decrease in hippocampal volume (16x) and increase in Tau and pTau181 concentration in the liquor (6x) compared to the BDNF rs6265 G/G genotype carriers, but the rate of β-amyloid accumulation in the cerebral cortex or β-amyloid 42 in the cerebrospinal fluid did not change [28]. The BDNF rs6265 gene A allele carriers at the preclinical stage of the disease have a high risk of the onset and progression of mild cognitive impairment or dementia within 12 years' period [29]. The BDNF rs6265 polymorphism should be considered as a potential factor influencing treatment and prevention outcomes of the disease. BDNF may be a female-specific risk gene for the development of Alzheimer's disease.

Currently, there are conflicting data regarding the relationship between the rs6265 polymorphic variant of the BDNF gene and changes in neurotrophin concentrations in schizophrenia [42]. No significant effect of genotypes of the rs65265 locus of the BDNF gene on serum protein levels was observed, but several studies reported a significant decrease [18] or conversely an increase [36] in its concentration in patients compared to the control group. It was found that carrying the A/A genotype of the BDNF rs6265 gene increases the risk of developing schizophrenia in European and Asian populations [15].

The probability of depression is significantly increased in individuals with the rs6265 polymorphism of the BDNF gene [30]. In addition, a modulating effect of such environmental factors as chronic stress, childhood abuse, and brain trauma on the association of the rs6265 locus of the BDNF gene with the risk of developing depressive disorder has been noted [2]. Lower neurotrophin concentrations were found in postmortem brain tissue samples from suicide victims, carriers of the BDNF rs6265 A allele, compared to healthy individuals [43]. In patients with psychoactive substance dependence, the rs6265 polymorphism of the BDNF gene through the processes of neuroplasticity can influence the duration of being in rehabilitation and the duration of remission [16, 35]. For example, in pharmacogenetic placebo-controlled studies of the efficacy of pregabalin for the treatment of alcohol dependence, it was found that the BDNF rs6265 A allele carriers dropped out of the treatment program earlier [16]. The BDNF rs6265 G/G genotype individuals who use only psychostimulants or with combined dependence on psychostimulants and cannabioids are able to stay in the rehabilitation program for a long time and have the longest remissions [35]. Besides, the rs6265 functional polymorphism of the BDNF gene has been shown to be a protective marker for family predisposition to addictive disorders [17].

While studying the rs6265 polymorphism of the BDNF gene, the G/A and A/A genotypes associated with a decrease in neuropsychic stability and professional reliability prevailed in the group of subjects systematically exposed to noise, vibration, barometric pressure variations, and other extreme factors [19]. The lowest risk of mental performance deterioration and the longest service record in the conditions of the Arctic zone are characteristic of military personnel with the BDNF rs6265 G/G genotype [23, 24]. Another study showed that 20% of flight personnel had a heterozygous G/A variant (rs6265) of the BDNF gene associated with low levels of neurotrophin and increased susceptibility to the development of psychoemotional stress [21]. This molecular genetic marker is necessary for the system of monitoring the mental health of persons in extreme professions and improving their professional training programs.

**The rs1800169 polymorphism of the CNTF gene.** The human CNTF gene is localized on the long arm of chromosome 11 in the 11q12.1 region, contains two exons and more than 2000 single nucleotide variants. Some studies have shown that the rs1800169 polymorphism of the CNTF gene is associated with an increased risk of neurologic diseases [11, 37]. Transition of G to A in position 6 of the acceptor splice site leads to CCAG insertion in the second exon, a shift of the reading frame and premature appearance of the stop codon in position 63. As a result of this mutation, the aberrant mRNA encodes a truncated protein consisting of 62 amino acids, which degrades rapidly after translation [39]. The frequency of occurrence of the CNTF rs1800169 minor allele in the Russian population is 18.9% and correlates with the data obtained when studying the population of European (14.5%), Asian (13.2%), and Latin American (11.5%) countries [20].

A few studies demonstrated a positive association of the carrier frequency of the CNTF rs1800169 polymorphism with the prevalence of schizophrenia spectrum disorders [40, 41]. R.C. Pierce

and A.A. Bari suggest that CNTF may enhance psychostimulant-induced behavioral sensitization that can form aspects of paranoid psychosis and drug craving [34]. The CNTF protein dysfunction in the developing brain is probably involved in delusional, schizoaffective, and bipolar disorders rather than in the development of schizophrenia [26].

P.-Y. Lin and G. Tsai did not confirm the association of this mutation with the risk of developing schizophrenia in a group of patients with a family history of psychiatric disorders; however, a significant association was found in a group of patients with no history of psychiatric disorders in their pedigrees compared to the control group [26]. A study by J. Nishiyama et al. did not provide evidence for the association of the CNTF rs1800169 polymorphic variant with the disorder as well as personality traits in the Japanese population [32]. J. Benkovits et al. also found no association of the CNTF rs1800169 polymorphism with the disorder in Hungarian patients compared to controls [1]. In a placebo-controlled study it was shown that the therapeutic effect of iloperidone is enhanced in patients with the CNTF rs1800169 G/G genotype [22]. The results suggest that the rs1800169 polymorphism of the CNTF gene does not affect the risk of schizophrenia in general, but it may play a more prominent role in its clinical manifestations. In addition, other mutations of this gene may also be involved in the pathogenesis of the disease.

R. Giess et al. found the CNTF rs1800169 A/A genotype in 2.4% of 288 individuals with multiple sclerosis and noted that carriers of this genotype are characterized by early onset of the disease with predominant motor disorders [10]. V. Hoffmann et al. found no significant correlation between the CNTF rs1800169 polymorphism and the age of patients at the onset of the disease, its course and severity [13]. This mutation is not a risk factor for the development of multiple sclerosis. The need in the CNTF protein for myelogenesis or cell survival can be replaced by excessive functional activity of other neurotrophic factors.

A negative association between the rs1800169 polymorphism of the CNTF gene and Alzheimer's disease has been confirmed in a number of studies [9, 11]. E. Grunblatt et al. reported that the disease developed in 17% of patients with mutant genotypes (A/A or G/A) and 25.2% of patients with normal genotype (G/G) of the rs1800169 locus of the CNTF gene. The presence of the CNTF rs1800169 G/G genotype presumably increases the risk of its occurrence [11].

According to N.N. Strambovskaya, patients with chronic cerebral ischemia have an increased frequency of the CNTF rs1800169 minor allele depending on the severity of the disease. The CNTF rs1800169 G/A genotype prevails in patients with chronic cerebrovascular insufficiency and increases the risk of its development 2.3 times. Weakening of the trophic action of CNTF probably leads to premature degeneration of nervous tissue, impaired integrity of the blood-brain barrier, and early onset of chronic vascular disease [37].

**Conclusion.** Lately a significant number of publications have been devoted to the identification of associations of polymorphic variants of the BDNF (rs6265) and CNTF (rs1800169) genes with the risk of development and features of the course of neurological disorders, as well as the effectiveness of drug therapy, with some data being contradictory. Sex, age, ethnicity, epigenetic processes and the presence of comorbid pathology affect the interpretation of the results. The issues of epistatic gene interaction require more detailed consideration. The problem of correlation between the contribution of genetic and environmental determinants remains unresolved and is still relevant. Further studies in this direction will help to clarify the role of single nucleotide variants of the BDNF and CNTF genes in various aspects of pathogenesis of nervous diseases and analyze genotypic and phenotypic heterogeneity in populations.

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