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Association of the carriage of *IL-1B rs1143634* and *rs16944* polymorphisms and *BDNF rs6265* polymorphism with temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is one of the most common and refractory forms of epilepsy, which has different etiologies. Experimental and clinical studies have demonstrated that transformation of the normal brain neuron activity pattern into paroxysmal one is accompanied by changes in the expression of cytokines and neurotrophins in the hippocampus and temporal cortex. Modulation of the expression of brain-derived neurotrophic factor (BDNF) may be associated with the carriage of the single nucleotide polymorphism (SNP) rs6265 in the BDNF gene. Groups of investigators have shown the increased expression of BDNF in the hippocampus and temporal cortex of patients with drug-resistant epilepsy. Independent studies have demonstrated the role of the IL-1B gene encoding the proinflammatory cytokine interleukin (IL) 1β in the development of inflammatory responses and structural mediobasal TLE with hippocampal sclerosis.

Objective: *to study the association of the carriage of the SNPs rs16944 and rs1143634 in the IL-1B gene and rs6265 in the BDNF gene with the development of TLE.*

Patients and methods. *Real-time polymerase chain reaction was used to conduct a molecular genetic study of the carriage of the SNPs rs1143634 and rs16944 in the IL-1B gene and rs6265 in the BDNF gene in 84 patients with TLE and in 203 healthy Caucasian volunteers, who lived in the Siberian Federal District.*

Results and discussion. *The carriage of the high-producing C allele (odds ratio (OR)=2.01; 95% confidence interval (CI), 1.31–3.08; p=0.001) and the homozygous CC genotype (OR=2.48; 95% CI, 1.47–4.17; p=0.001) of SNP rs1143634 in the IL-1B gene was found to be statistically significantly associated with the development of TLE in the examined population. There were no statistically significant differences in the carriage of the SNPs rs1143634 and rs16944 in the IL-1B gene and rs6265 in the BDNF gene with the clinical presentations and course of TLE (p>0.05). The carriage of the SNP rs6265 in the BDNF gene was ascertained to be unassociated with the development of TLE (χ^2=0.3; p =0.86).*

Conclusion*. The authors have established an association of the carriage of the high-producing C allele and the homozygous CC genotype of the SNP rs1143634 in the IL-1B gene with TLE.*

Keywords: *temporal lobe epilepsy; IL-1B; BDNF; single nucleotide polymorphism; cytokine; neurotrophin.*
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Temporal lobe epilepsy (TLE) is a multifactorial neurological disease with a high risk of drug resistance. The proportion of TLE is high in adults and children and accounts for 25% of all cases of epilepsy, and among focal forms it is about 60%. One of the most common causes of TLE is hippocampal sclerosis, which often determines the need for surgical intervention [1–2]. It was shown that the transformation of the normal pattern of neuron activity into a paroxysmal one is accompanied by changes in the expression of cytokines in the hippocampus and temporal cortex, including interleukin (IL) 1β and neurotrophic brain factor (Brain–Derived Neurotrophic Factor, BDNF) linked with the membrane-associated tyrosine kinase receptor B, encoded by the gene NTRK2 [3–4].

Proinflammatory cytokines are highly integrated markers both in patients with drug resistant epilepsy and in experimental animal models of epilepsy [5]. The IL1B gene, encoding the proinflammatory cytokine IL1β, plays a role in the development of inflammatory reactions and is a genetic predictor of mesial temporal sclerosis and mediobasal temporal lobe epilepsy [6]. N.V. Terskova et al. [7] found that the highly producing SNP *3954 * C* of the IL1B gene predisposes to an increased synthesis of the cytokine of the same name, development and progression of chronic adenoiditis in children. According to N.A. Schneider et al. [8] and M.A. Stroganova et al. [9], the SNP *rs1143634* of the *IL1B* gene is associated with a high risk of developing febrile seizures in carriers of the high-producing allele C. This agrees with the published data, according to which the genotype *CT rs1143634* of the *IL1B* gene leads to a higher level of IL1β in the cerebrospinal fluid and the associated increased risk of development of post-traumatic epilepsy; carriers of the homozygous *TT* genotype of the *IL1B* gene, by contrast, are less likely to develop post-traumatic epilepsy [10].

Particular attention in the development of TLE is given to BDNF, a neurotrophin that promotes growth, survival and differentiation of neurons, as well as synaptic plasticity in various areas of the brain, especially in the hippocampus. Thus, an increased

expression of BDNF in the hippocampus and temporal cortex has been shown in patients with drug resistant epilepsy during seizures [4]. The SNP *rs6265* of the *BDNF* gene is a functionally relevant polymorphism that is associated with the secretion of BDNF and the hippocampus volume [11].

The purpose of the research is to study the association of the carriage of the SNPs rs16944 and rs1143634 of the *IL1B* gene and rs6265 of the BDNF gene with the development of temporal lobe epilepsy.

Patients and methods. The study was approved at a meeting of the Local Ethics Committee of V.F. Voyno-Yasenetsky Krasnoyarsk State Medical University (KrasSMU) on the 27th of September 2018, planned and carried out in accordance with the Helsinki Declaration. All patients with temporal lobe epilepsy and healthy volunteers included in the study signed voluntary informed consent.

The study involved 287 Caucasian residents living in the Siberian Federal Region. Patients for the study were selected according to stratified randomization methods using inclusion and exclusion criteria. The 1st (main) group included patients with TLE. *Inclusion criteria:* residents of the Siberian Federal Region; age 10 to 75 years; verified diagnosis of temporal lobe epilepsy. *Exclusion criteria:* residents of other regions; presence of marked cognitive impairment; patient's refusal to participate in the clinical study. The 2nd (control) group included healthy volunteers. *Inclusion criteria:* healthy people aged 10 to 75 years, residents of the Siberian Federal Region. *Exclusion criteria:* presence of epilepsy, subclinical epileptiform changes on the electroencephalogram (EEG); presence of marked cognitive impairment; residents of other regions; refusal to participate in the study.

The following research methods were used: anamnestic, neurological, laboratory (molecular genetic), neurophysiological (video-EEG-monitoring), neuroradiological (MRI of the brain with a magnetic field power of at least 1.5 T, performed according to the Epilepsy protocol, including proton magnetic resonance spectroscopy of the hippocampus).

Characteristics of patients with TLE are presented in Table 1. In the 1st group there were 28 (33%) males and 56 (67%) females, the 2nd group (control) included 55 (27%) males and 149 (73%) females.

Molecular genetic research was performed on the basis of the Interdepartmental Laboratory of Medical Genetics of the Department of Medical Genetics and Clinical Neurophysiology of V.F. Voyno-Yasenetsky KrasSMU. Blood for analysis was taken from the cubital vein in a volume of 10 ml into vacuum tubes containing 0.5 M solution of ethylenediaminetetraacetic acid. Genomic DNA was isolated from 0.1 ml of leukocyte suspension by the sorption method using the «DNA-Sorb-B» (AmpliPrime, Russia). The carriage of SNPs *rs1143634* and *rs16944* of the *IL1B* gene and *rs6265* of the *BDNF* gene was determined by means of real-time polymerase chain reaction using Rotor-Gene 6000 diagnostic equipment (Corbett Life Science, Australia) and TaqMan allelic discrimination technology; carriage of SNPs *rs1143634* and *rs16944* of the *IL1B* gene – using Applied Biosystems (USA) fluorescent probes and *rs6265* of the *BDNF* gene – using Syntol fluorescent probes (Russia). SNPs *rs1143634* and *rs16944* of the *IL1B* gene were studied in 84 patients with temporal lobe epilepsy (1st group) and 203 healthy volunteers (2nd group), and SNP *rs6265* of the *BDNF* gene – in 83 patients with temporal lobe epilepsy (1st group) and 194 healthy volunteers (2nd group).

Statistical analysis was performed using SPSS Statistics application packages (Version 22.0) and the «Gene Expert» online calculator, (http://gen-exp.ru/calculator_or.php). Significance of differences between the quality indices of independent samples was evaluated by the nonparametric criterion χ^2. To assess the quality indices we used exact one-sided Fisher criterion. The risk of developing temporal lobe epilepsy was assessed by odds ratio (OR; 95% confidence interval, CI). Significance of differences between indices of independent samples (n> 30) was determined by unpaired t-test. Qualitative variables were expressed as numbers and percentages; quantitative variables – as both mean and standard deviation (Mean ± SD).

Results. *The study of the carriage frequency of SNPs rs16944 and rs1143634 of the IL1B gene.* The carriage frequency of the allele *C rs16944* of the *IL1B* gene in individuals with TLE was 69.6%, in healthy volunteers 63.3% (OR 1.33; 95% CI 0.9–1.96); the carriage frequency of the allele *T rs16944* of the *IL1B* gene was 30.4% and 36.7%, respectively (OR 0.75; 95% CI 0.51–1.11); the carriage rate of the homozygous *CC* genotype was 47.6% and 38.9% (OR 0.43; 95% CI 0.85–2.38); heterozygous CT genotype – 44% and 48.8% (OR 0.83; 95% CI 0.50–1.38); TT genotype – 8.3% and 12.3% (OR 0.65; 95% CI 0.27–1.56). There were no statistically significant differences in the carriage frequency of alleles (_2 = 2.11; p = 0.15) and genotypes (χ^2 = 2.21; p = 0.33) SNPs *rs16944* of the *IL1B* gene in the compared groups.

The carriage frequency of alleles and genotypes *rs1143634* of the *IL1B* gene in the 1st and 2nd groups is presented in Table 2. In patients with temporal lobe epilepsy, the carriage of the allele *C* (χ^2 = 10.36; p = 0.001) and the homozygous genotype *CC rs1143634* of the *IL1B* gene (χ^2 = 13.1; p = 0.001) was more frequently statistically significant. Thus, it has been shown that the carriage of the *C* allele (OR = 2.01; 95% CI 1.31–3.08) and the homozygous CC genotype (OR = 2.48; 95% CI 1.47–4.17) is a risk factor for temporal lobe epilepsy development.

Study of the carriage frequency of SNP rs6265 of the BDNF gene. Carriage frequency of the allele G in the patients of the 1st group was 83%, in the participants of the 2nd group – 85% (OR 0.87; 95% CI 0.53–1.42); the allele *A* – 17% and 15%, respectively (OR 1.15; 95% CI 0.71–1.89). The carriage of *GG, GA, AA* genotypes in the patients in the 1st group was found in 71%, 24% and 5% of cases, respectively; and in the 2nd group – in 74%, 22% and 4% of cases, respectively. The OR for the homozygous *GG* genotype was 0.85 (95% CI 0.46–1.51), for the *GA* genotype – 1.15 (95% CI 0.63-2.11), for the *AA* genotype – 1.18 (95% CI 0.34–4.02). No statistically significant differences in the carriage frequency of the alleles (χ^2 = 0.33; p = 0.57) and genotypes (χ^2 = 0.3; p = 0.86) *rs6265* of the *BDNF* gene were revealed in the compared groups (p> 0.05).

The study of the association of the carriage of SNPs of the IL1B and BDNF genes with the clinical characteristics of temporal lobe epilepsy. While analyzing the haplotype carriage of the SNPs *rs16944* and *rs1143634* of the *IL1B* gene, we found that the carriage of the *CT / CT* haplotype was more common in patients with temporal lobe epilepsy receiving monotherapy with AEDs (23.7%), which is probably due to the protective effect of low-producing T allele in this heterozygote (p = 0.012; χ^2 6.37). While analyzing the association of haplotypes of SNPs *rs16944* and *rs1143634* of the *IL1B* gene with clinical features of temporal lobe epilepsy (remission of epileptic seizures, the presence of drug resistance and the course of the disease), no statistically significant differences were observed (p> 0.05).

Table 1. Clinical and anamnestic characteristics of patients of the 1st group (n = 84).

Characteristic	The number of observations, n (%)
Mean age, years, M±SD	36.6±14.6*
Average duration of the disease, years, M±SD:	15.5±11.04*
Absolute duration of the disease, years:	
>10	45 (54)
5–10	26 (31)
<5	13 (15)
Average debut age of epilepsy, years, M±SD	19.6±14.6*
Controllability of epilepsy:	
compensated course	20 (23.8)
uncompensated course	64 (76.2)
drug resistance	21 (25)
Febrile seizures in history:	
absence	76 (90)
presence	8 (10)
Neuroimaging:	
lack of structural changes	9 (11)
structural changes	75 (89)
Type of antiepileptic therapy:	
monotherapy with AEDs	39 (46.4)
polytherapy with AEDs	45 (53.6)
Surgical treatment of epilepsy in history:	
not conducted	75 (89)
conducted	9 (11)

Note. AEDs - antiepileptic drugs

Table 2. Carriage frequency of SNPs *rs1143634* of the *IL1B* gene in patients with temporal epilepsy compared with healthy controls

rs1143634	Main group, n=84	Control group, n=203	χ^2	*p*	OR	
					abs.	95% CI
Allele:						
C	0.8	0.66	10.36	**0.001**	**2.01**	**1.31–3.08**
T	0.2	0.34			0.5	0.32–0.77
Genotype:						
CC	0.61	0.38	13.12	**0.001**	**2.48**	**1.47–4.17**
CT	0.38	0.56			0.49	0.29–0.82
TT	0.01	0.06			0.19	0.02–1.5

Statistically significant differences in the carriers of SNPs of the *IL1B* and *BDNF* genes regarding the development of mesial temporal sclerosis, clinical and anamnestic features of temporal lobe epilepsy (history of febrile seizures, efficacy and type of pharmacotherapy, epilepsy) have not been found (p> 0.05).

Discussion. Interleukin IL1β is one of the most frequently studied proinflammatory cytokines for assessing and predicting the outcomes of the inflammatory processes in patients with drug resistant epilepsy [3, 5], because it changes the blood-brain barrier permeability and neuronal excitability due to increased glutamatergic transmission and proconvulsive action. The specific role of IL1β in the genesis of epilepsy is due to its expression not only in peripheral tissues, but also in the CNS, where in astrocytes and microglia it acts as a factor of chronic inflammation caused by various reasons (traumatic brain injury, infections, etc.) [10, 12]. Thus, increased expression of IL1β in the hippocampus and the anterior temporal cortex was confirmed by immunohistochemical studies in brain samples obtained from patients after surgical treatment [13–15]. In patients with mediobasal temporal lobe epilepsy and hippocampal sclerosis, overexpression of IL1β was detected in serum [16]. An elevated level of IL1β in the cerebrospinal fluid in patients with epilepsy indicates damage to the blood-brain barrier and systemic inflammation [17]. A number of point markers of a high-producing allelic variant of the *IL1B* gene, which are more often inherited by linkage (*3953, -3737, -1469, -999*), were identified. In the individuals who are homozygous or heterozygous for the highly producing allele *C* (*3953 C_T*), the production of the cytokine IL1β is respectively twice and four times higher than in those who are homozygous for the low producing allelic variant (*IL1B * 1*) [18]. In our study, the carriage of the highly producing allele C and the homozygous *CC* genotype of the SNP *rs1143634* of the *IL1β* gene was statistically significantly associated with the development of temporal lobe epilepsy. While analyzing the foreign and domestic literature, we did not encounter any reports on the association of this SNP with the risk of temporal lobe epilepsy, although the prognostic role of *rs1143634* of the *IL1B* gene was studied in patients with post-traumatic epilepsy [19, 20]. According to B.Leal et al. [21], the carriage of the homozygous *TT* genotype (*rs16944*) was more often observed in patients with mediobasal temporal lobe epilepsy and sclerosis of the hippocampus (p = 0.021). K.A. Lehtimäki et al. [22] also showed that carriers of the *511T* allele of the *IL1B* gene have an increased susceptibility to the development of drug resistant forms of epilepsy. However, in our study, in patients with temporal lobe epilepsy and hippocampal sclerosis an association of drug resistance with the carriage of SNPs rs1143634 and *rs16944* of the *IL1B* gene was not identified, which may be due to a small sample of patients with hippocampal sclerosis.

In many neurological and mental diseases, dysregulation of neurotrophins, BDNF in particular, has been noted. Researchers

have observed the anticonvulsant and neuroprotective effects of neurotrophic factors, including BDNF, which stimulates the development of nerve cells in the CNS and peripheral nervous system, helps maintain the survival of existing neurons, and promotes the growth and differentiation of new neurons and synapses [23]. At the same time, increased expression of BDNF in the hippocampus, temporal cortex in patients with drug resistant epilepsy, as well as in an animal model of epilepsy has been described [4, 24]. A decrease in the level of BDNF in the serum and plasma of adult patients with epilepsy has been shown [25]. Recently, an increase in the expression of BDNF has been considered the necessary condition for epileptogenesis; it can occur under the influence of an epileptic seizure and leads to activation of the tyrosine kinase receptor (TrkB) of the neurotrophic factor of the brain [26].

The SNP *rs6265* of the *BDNF* gene which we studied is a functionally relevant polymorphism that is associated with the secretion of BDNF and the volume of the hippocampus [27]. A large amount of research suggests that *rs6265* is the most common polymorphism of the *BDNF* gene, which may contribute to the development of epilepsy. This polymorphism affects a decrease in the activity of BDNF-dependent secretion, dramatically changing the intracellular transport and packaging of BDNF, which may be associated with an increased risk of neuropsychiatric disorders [27]. N. Shen et al. [11] found that SNP *rs6265* (*196G_A*) can play an important role in epileptogenesis, and the carriage of the allele A plays a protective role in the development of epilepsy. In addition, in the systematic review by Y.L. Xu et al. [28] it was shown that the considered SNP is associated with the development of epilepsy, but in the works including patients with temporal lobe epilepsy [29] and hippocampal sclerosis, no association was found between the carriage of the alleles *G* and *A* (rs6265) and clinical markers of the disease [30]. According to our data, there were no statistically significant differences between carriers of SNP *rs6265* of the *BDNF* gene and healthy individuals (controls).

Conclusion. Thus, the carriage of the highly producing allele C and the homozygous *CC* genotype (*rs1143634*) of the *IL1B* gene is statistically significantly associated with a high risk of developing temporal lobe epilepsy. The carriage of the haplotype *CT / CT* (*rs1143634* and *rs16944*) of the *IL1B* gene has a statistically significant influence on the effectiveness of monotherapy with AEDs, which is probably due to the protective effect of the low-producing T allele in this heterozygous association. In patients with TLE and hippocampal sclerosis, no association with the carriage of SNPs *rs1143634* ($p = 0.62$), *rs16944* ($p = 0.29$) of the *IL1B* gene was detected. The association of carriage of SNP *rs6265* of the *BDNF* gene with the development of TLE and clinical and anamnestic features of the disease course was not detected. However, it is still necessary to conduct multicenter studies with larger patient samples and assessment of the results of neuroimaging to determine the clinical role of the carriage of SNPs of the *IL1B* and *BDNF* genes.

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