Study of the role of carriage of single nucleotide variants of the *IL-1β*, *TNFA*, *BDNF*, *NTRK-2* genes in the development and clinical features of temporal lobe epilepsy

Panina Yu.S., Domoratskaya E.A., Paramonova A.I., Dmitrenko D.V.
V.F. Voyno-Yasenetsky Krasnoyarsk Medical State University, Ministry of Health of Russia, Krasnoyarsk
1, Partizana Zheleznyaka St., Krasnoyarsk 660022, Russia

Temporal lobe epilepsy (TE) is the most common form of focal epilepsy in adults with a high rate of drug-resistant course. In the Russian Federation studies of the contribution of the carriage of single nucleotide variants of genes (SNGs) encoding proteins of neuroinflammation and neurodegeneration to the development of TE have not been previously carried out.

Objective: *to study the association of SNGs rs16944 and rs1143634 of the IL-1β gene, rs1800629 of the TNFA gene, rs6265 of the BDNF gene, rs3780645 of the NTRK-2 gene with the risk of development, clinical and neuroimaging features of TE.*

Patients and methods. *The study included 166 patients with TE and 203 healthy volunteers living in the Siberian Federal District. The study included clinical, neurophysiological, neuroradiological, and laboratory work-up. Investigation of the carriage of SNGs rs16944 (-511T/C) and rs1143634 (+3954C/T) of the IL-1β gene, rs1800629 (G-308A) of the TNFA gene, rs6265 (G/A) of the BDNF gene, rs3780645 (C/T) and rs2289656 (C/T) of the NTRK-2 gene was carried out by real-time polymerase chain reaction.*

Results and discussion. *The prognostically unfavorable role of carriage of the A allele and the GA rs1800629 genotype of the TNFA gene in the development of TE, the GA rs6265 genotype of the BDNF gene in the development of TE with hippocampal sclerosis was established. Carrying the genotype AA rs1800629 of the TNFA gene in patients with TE reduces the risk of polytherapy with antiepileptic drugs.*

Conclusion. *The study of neuroinflammation and neurodegeneration processes is important both from a physiological point of view and from the point of view of searching for the TE development markers, which make it possible to predict and evaluate the rate of disease progression, help to determine the tactics of treatment, and evaluate its effectiveness. In this regard, at present, the identification of potential genetic markers remains a task of high priority.*

Keywords: *temporal lobe epilepsy; IL-1β; TNFA; BDNF; NTRK-2; single nucleotide polymorphism; gene; pharmacoresistance.*
Contact: *Ekaterina Alekseevna Domoratskaya;* ***e.domorats@yandex.ru***
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Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy in adults [1, 2]. In 40% of patients, epileptic seizures are refractory to drug therapy [3–5].

Experimental and clinical data indicate that neuroinflammatory and neurodegenerative processes can reinforce each other, contributing to the onset and chronic course of epilepsy, as well as the formation of drug resistance [6–9]. Protein biomarkers of inflammation and neurodegeneration in TLE have been studied in experimental models, in the hippocampal tissue of patients with resistant forms of TLE, in the patients' blood or cerebrospinal fluid [10–12].

Studies of the contribution of the carriage of single nucleotide polymorphisms (SNP) of genes encoding neuroinflammation and neurodegeneration proteins to the development of TLE have been actively carried out for several years, but such studies have not been previously conducted in the Russian Federation [13, 14].

Objective: To study the association of carriage of SNPs rs16944 and rs1143634 of the *IL-1β* gene, rs1800629 of the *TNFA* gene, rs6265 of the *BDNF* gene, rs3780645 of the *NTRK-2* gene with the risk of development, and clinical and neuroimaging features of TLE.

Patients and methods. The study was approved by the local Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education «Prof. V.F. Voino-Yasenetsky Krasnoyarsk State Medical University» of the Ministry of Health of the Russian Federation (protocol No. 85/2018 dated September 27, 2018). All patients signed a voluntary informed consent.

The study included 166 patients with mesial TLE and 203 healthy volunteers.

Inclusion criteria in the main group: patients with mesial TLE; age from 16 to 80 years; residents of the Siberian Federal District; voluntarily signed informed consent. *Exclusion criteria:* patients with other forms of epilepsy; lack of voluntarily signed informed consent; an increase in body temperature at the time of the study above 36.9°C; acute diseases or exacerbation of chronic diseases within one month before the study.

Inclusion criteria in the control group: healthy people; age from 16 to 80 years; voluntarily signed informed consent.

Exclusion criteria: the presence of neuropsychiatric diseases; subclinical epileptiform changes on the EEG; an increase in body temperature at the time of the study above 36.9°C; acute diseases or exacerbation of chronic diseases within one month before the study; lack of voluntarily signed informed consent.

The study included clinical (history analysis, examination of the neurological status, assessment of the severity of epileptic seizures using the National Hospital Epileptic Seizure Severity Scale), neurophysiological (EEG video monitoring); neuroradiological (brain MRI), and laboratory (biochemical, molecular, genetic) investigation methods.

Molecular genetic studies were carried out in the laboratory of medical genetics using the instrumental base of the Center for Collective Use of the Federal State Budgetary Educational Institution of Higher Education «Prof. V.F. Voino-Yasenetsky Krasnoyarsk State Medical University» of the Ministry of Health of the Russian Federation.

The study of carriage of SNPs was carried out by real-time polymerase chain reaction (RT-PCR) on a Rotor-Gene 6000 apparatus (Corbett Life Science, Australia) using TaqMan allelic discrimination technology and Applied Biosystems (USA) fluorescent probes for rs16944 (-511T/ C) and rs1143634 (+3954C/T) of the *IL-1β* I gene, rs1800629 (G-308A) of the *TNFA* gene; and Synthol (Russia) for rs6265 (G/A) of the *BDNF* gene, rs3780645 (C/T) of the *NTRK-2* gene.

Blood sampling from patients was performed from the cubital vein into IMPROVACUTER vacuum tubes (Guangzhou Improve Medical Instruments, China) containing 0.5 M of ethylenediaminetetraacetic acid (EDTA) solution. Isolation of genomic DNA from 0.1 ml of leukocyte suspension was carried out by the sorption method using the DNA-Sorb-B kit (103-20, AmpliPrime, Russia) according to the manufacturer's instructions. The isolated DNA was stored at -20°C. The RT-PCR buffer included a 2.5-fold reaction mixture adapted for RT-PCR, 25 mM of MgCl2, ddH2O (M-428, Sintol, Russia).

Statistical Methods. Based on the results of the study, a database was formed in MS Excel 2013, on the basis of which statistical analysis was carried out using the SPSS Statistics software package (version 19.0). The median (Me) and interquartile range [25th; 75th percentile] were used for the description of the quantitative data with non-normal distribution. The 95% confidence interval (95% CI) was used to describe qualitative data. To compare several groups on a quantitative basis, nonparametric analysis of variance (Kruskell–Wallis test) was used, followed by pairwise comparisons of groups with each other; the Mann–Whitney test was used to compare the two groups. To determine the statistical significance of differences between the qualitative traits, Pearson's chi-square test (χ^2) was used for expected frequencies greater than 5. To assess risk factors associated with the development of TLE, odds ratio (OR, 95% CI) or risk ratio (RR, 95% CI) were assessed. Spearman's correlation coefficient (r) was used to assess the relationship between quantitative traits with non-normal distribution. Intergroup differences were recognized as statistically significant at $p<0.05$.

Results. The age of patients with TLE in the study group at the time of the study ranged from 16 to 76 years; median age was 35.0 [29.0; 46.0] years. Distribution of patients by gender: males – 69 (41.6%), females – 97 (58.4%). The age of onset of TLE was 19.0 [13.0; 30.5] years. The duration of the disease in 54% (89/166) of cases exceeded 10 years, the median was 11.0 [9.0; 20.0] years.

In 74.7% of cases (124/166) bilateral tonic-clonic seizures with a focal onset were recorded. The severity of epileptic seizures according to the National Hospital Scale ranged from 1 to 23 points, the median was 13.0 [11.0; 16.0] points.

Table 1. *Frequencies of SNGs alleles of IL-1β, TNFA, BDNF, NTRK-2 genes*

Gene	SNP	Nucleotide substitution	Allele frequency in the European population, %	Allele frequency in the study population, %
IL-1β	rs16944	-511T/C	65,7	67,4
IL-1β	rs1143634	+3954C/T	24,0	23,7
BDNF	rs6265	G/A	18,9	17,1
NTRK-2	rs3780645	(C/T)	3,9	4,8
TNFA	rs1800629	(G-308A)	16,5	12,9

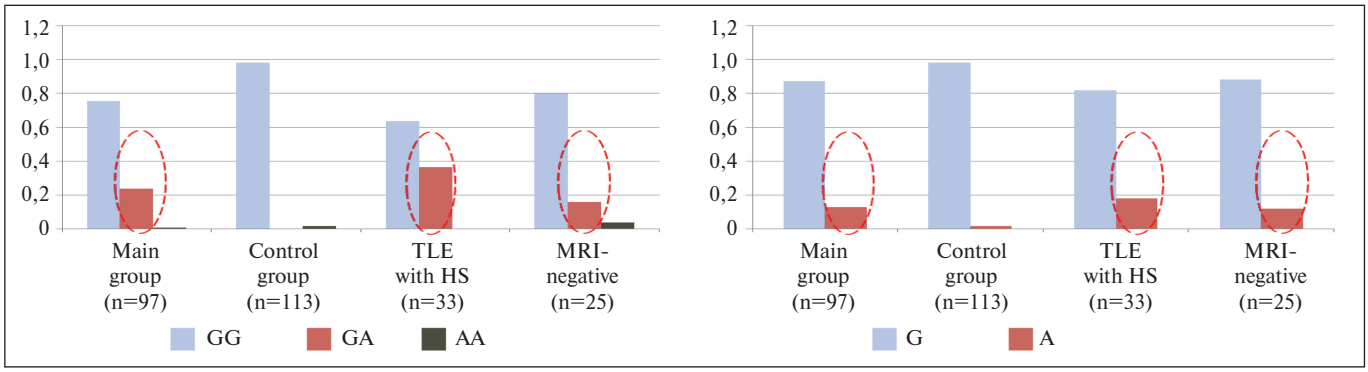

Fig. 1. *The frequency of carriage of alleles and genotypes of the rs1800629 of the TNFA gene in patients with TE and in the control group*

Table 2. *Frequency of carriage of genotypes and alleles of the rs1800629 of the TNFA gene in the groups of comparison*

Alleles, genotypes	Number of examined participants, n (%) main group (n=97) 1	control group (n=113) 2	TLE with HS (n=33) 3	MRI-negative TLE (n=25) 4	χ^2; p	OR/RR; 95% CI
G	169 (87,1)	111 (98,2)	27 (81,8)	22 (88)	$\chi^2_{1,2}$=10,035; $p_{1,2}$=0,002*; $\chi^2_{2,3}$=13,283; $p_{2,3}$<0,001*; $\chi^2_{2,4}$=6,135; $p_{2,4}$=0,014*; $\chi^2_{3,4}$=0,415; $p_{3,4}$=0,52	$OR_{1,2}$=0,12; 95% $CI_{1,2}$ 0,03–0,56 $OR_{2,3}$=0,08; 95% $CI_{2,3}$ 0,02–0,42 $OR_{2,4}$=0,13; 95% $CI_{2,4}$ 0,02–0,84 $OR_{3,4}$=1,63; 95% $CI_{3,4}$ 0,37–7,27
A	25 (12,9)	2 (1,8)	6 (18,2)	3 (12)		$OR_{1,2}$=8,21; 95% $CI_{1,2}$ 1,8–37,51 $OR_{2,3}$=12,33; 95% $CI_{2,3}$ 2,36–64,52 $OR_{2,4}$=7,57; 95% $CI_{2,4}$ 1,19–47,98 $OROR_{3,4}$=0,61; 95% $CI_{3,4}$ 0,14–2,74
GG	73 (75,9)	111 (98,2)	21 (63,6)	20 (80)	$\chi^2_{1,2}$=30,137; $p_{1,2}$<0,001*; $\chi^2_{2,3}$=45,056; $p_{2,3}$<0,001*; $\chi^2_{2,4}$=19,265; $p_{2,4}$<0,001*; $\chi^2_{3,4}$=2,452; $p_{3,4}$=0,294	$OR_{1,2}$=0,06; 95% $CI_{1,2}$ 0,01–0,4 $OR_{2,3}$=0,03; 95% $CI_{2,3}$ 0,01–0,15 $OR_{2,4}$=0,07; 95% $CI_{2,4}$ 0,01–0,4 $OR_{3,4}$=0,23; 95% $CI_{3,4}$ 0,04–1,36
GA	23 (22,5)	0	12 (36,4)	4 (16)		$RR_{1,2}$=2,51; 95% $CI_{1,2}$ 2,11–3,0 $RR_{2,3}$=6,38; 95% $CI_{2,3}$ 4,31–9,45 $RR_{2,4}$=6,38; 95% $CI_{2,4}$ 4,31–9,45 $OR_{3,4}$=2,33; 95% $CI_{3,4}$ 0,45–12,23
AA	1 (1,6)	2 (1,8)	0	1 (4)		$OR_{1,2}$=1,23; 95% $CI_{1,2}$ 0,05–6,48 $RR_{2,3}$=4,36; 95% $CI_{2,3}$ 3,23–5,89 $OR_{2,4}$=2,31; 95% $CI_{2,4}$ 0,20–26,55 $RR_{3,4}$=6,5; 95% $CI_{3,4}$ 3,11–13,57
HWE, χ^2 (p)	0,305 (p=0,58)	113 (p=0)	1,63 (p=0,202)	1,469 (p=0,225)		

Note. Here and in tables 3 and 4: * – differences are statistically significant.

Structural etiology of TLE was identified in 51.8% of cases. According to the results of the analysis of brain MRI data, patients with TLE were divided into three groups: TLE with hippocampal sclerosis (HS) – 62 (37.4%); without structural changes in the brain (MRI-negative) – 40 (24.1%); with other structural changes – 64 patients (38.6%; excluded from the subsequent analysis).

Carriage frequency of SNP alleles of the *IL-1β*, *TNFA*, *BDNF*, *NTRK-2* genes among the patients with TLE living in the Krasnoyarsk Territory and the European population according to the international Genome Aggregation Database (gnomAD; available at: https://gnomad.broadinstitute.org/) is presented in Table 1. The distribution of allele and genotype frequencies of the studied SNPs in genes *IL-1β*, *TNFA*, *BDNF*, *NTRK-2* corresponds to Hardy–Weinberg equilibrium (HWE).

Molecular genetic analysis revealed a statistically significant association of carriage of the rs1800629 allele A of the *TNFA* gene with the development of TLE (OR=8.21; 95% CI 1.8–37.51; χ^2=10.035; p=0.002).

Carrying the genotype GA increases the risk of developing TLE by 2.52 times (RR=2.51; 95% CI 2.11–3.0; χ^2=30.137; p<0.001). Also, carriage of the A allele and genotype GA rs1800629 of the *TNFA* gene is associated with the development of TLE with HS (OR=12.33; 95% CI 2.36–64.52; χ^2=13.283; p<0.001 and RR=6.38; 95% CI 4.31–9,45; χ^2=45.056; p<0.001, respectively). A statistically significant association with the development of MRI-negative TLE was found for carriers of the A allele (OR=7.57; 95% CI 1.19–47.98; χ^2=6.135; p=0.014) and genotype GA (RR=6.38; 95% CI 4.31–9.45; χ^2=19.265; p<0.001) rs1800629 of the TNFA gene compared with the control group (Fig. 1; Table 2).

Carriage of the genotype AA rs1800629 of the *TNFA* gene is associated with the type of pharmacotherapy (mono- or polytherapy) for TLE (RR=4.82; 95% CI 1.71–13.61; p=0.003); reduces the risk of polytherapy with antiepileptic drugs (AED) by 4.82 times (Table 3).

A statistically significant association of the carriage of the GA genotype rs6265 of the *BDNF* gene with the development of TLE with HS (OR=2.22; 95% CI 1.17–4.18; χ^2=6.662; p=0.036) was found in comparison with the control group (Table 4).

Table 3. *Association of carriage of the genotypes rs1800629 of the TNFA gene with TE pharmacotherapy*

Genotype	Number of examined participants, n (%) monotherapy (n=51)	polytherapy (n=46)	χ^2	p	RR; 95% CI
AA	45 (88,2)	28 (60,9)	12,081	0,003*	4,82; 95% CI 1,71–13,61
GA	5 (9,8)	18 (39,1)			0,17; 95% CI 0,06–0,51
GG	1 (2)	0			1,92; 95% CI 1,59–2,33

Table 4. *Frequency of carriage of rs6265 genotypes and alleles of the BDNF gene in the comparison groups*

Genotype	Number of examined participants, n (%) main group (n=158) 1	control group (n=201) 2	TLE with HS (n=58) 3	MRI-negative TLE (n=39) 4	χ^2; p	OR; 95% CI
AA	5 (3,2)	8 (4)	3 (5,2)	1 (2,6)	$\chi^2_{1,2}$=2,772; $p_{1,2}$=0,251; $\chi^2_{2,3}$=6,662; $p_{2,3}$=**0,036***; $\chi^2_{2,4}$=0,77; $p_{2,4}$=0,681; $\chi^2_{3,4}$=5,899; $p_{3,4}$=0,053	$OR_{1,2}$=0,789; 95% $CI_{1,2}$ 0,25–2,46 $OR_{2,3}$=1,32; 95% $CI_{2,3}$ 0,34–5,13 $OR_{2,4}$=0,64; 95% $CI_{2,4}$ 0,08–5,23 $OR_{3,4}$=1,17; 95% $CI_{3,4}$ 0,048–4,82
GA	44 (27,9)	41 (20,4)	21 (36,3)	6 (15,4)		$OR_{1,2}$=1,51; 95% $CI_{1,2}$ 0,92–2,46 $OR_{2,3}$=2,22; 95% $CI_{2,3}$ 1,17–4,18 $OR_{2,4}$=0,71; 95% $CI_{2,4}$ 0,28–1,81 $OR_{3,4}$=0,32; 95% $CI_{3,4}$ 0,12–0,89
GG	109 (68,9)	152 (75,6)	34 (58,6)	32 (82)		$OR_{1,2}$=0,72; 95% $CI_{1,2}$ 0,45–1,14 $OR_{2,3}$=0,42; 95% $CI_{2,3}$ 0,22–0,78 $OR_{2,4}$=1,47; 95% $CI_{2,4}$ 0,61–3,55 OR3.4=3,23; 95% $CI_{3,4}$ 1,22–8,52
HWE, χ^2 (p)	0,047 (p=0,828)	5,266 (p=0,022)	0,011 (p=0,917)	1,053 (p=0,305)		

A statistically significant association between the carriage of SNPs rs16944, rs1143634 of the *IL-1β* gene, as well as rs3780645 of the NTRK-2 gene and the development of TLE was not revealed (p>0.05; Table 5).

Table 5. *Frequency of carriage of the genotypes rs16944, rs1143634, rs1143627 of the IL-1β gene, rs3780645 and rs2289656 of the NTRK-2 gene in groups of comparison*

Genotype	Number of examined participants, n (%) main group 1	control group 2	χ^2; p	OR; 95% CI
		rs16944 (-511C/T) of the IL-1β gene		
	(n=158)	**(n=203)**		
SS	68 (43,1)	79 (38,9)	$\chi^2_{1,2}$=1,781; $p_{1,2}$=0,411	$OR_{1,2}$=1,19; 95% $CI_{1,2}$ 0,78–1,81
ST	77 (48,7)	99 (48,8)		$OR_{1,2}$=0,99; 95% $CI_{1,2}$ 0,66–1,51
TT	13 (8,2)	25 (12,3)		$OR_{1,2}$=0,64; 95% $CI_{1,2}$ 0,32–1,29
HWE, χ^2 (p)	1,88 (p=0,17)	0,5 (p=0,479)		
		rs1143634 (+3954C/T) of the IL-1β gene		
	(n=158)	**(n=203)**		
SS	89 (56,3)	113 (55,7)	$\chi^2_{1,2}$=0,851; $p_{1,2}$=0,654	$OR_{1,2}$=1,03; 95% $CI_{1,2}$ 0,68–1,56
ST	63 (39,9)	78 (38,4)		$OR_{1,2}$=1,06; 95% $CI_{1,2}$ 0,64–1,63
TT	6 (3,8)	12 (5,9)		$OR_{1,2}$=0,628; 95% $CI_{1,2}$ 0,23–1,71
HWE, χ^2 (p)	1,623 (p=0,202)	0,092 (p=0,762)		
		rs3780645 (C/T) of the NTRK-2 gene		
	(n=135)	**(n=196)**		
SS	122 (90,4)	180 (91,8)	$\chi^2_{1,2}$=0,215; $p_{1,2}$=0,643	$OR_{1,2}$=0,83; 95% $CI_{1,2}$ 0,39–1,8
ST	13 (9,6)	16 (8,2)		$OR_{1,2}$=1,2; 95% $CI_{1,2}$ 0,56–2,58
TT	0			–
HWE, χ^2 (p)	0,345 (p=0,557)	0,355 (p=0,551)		

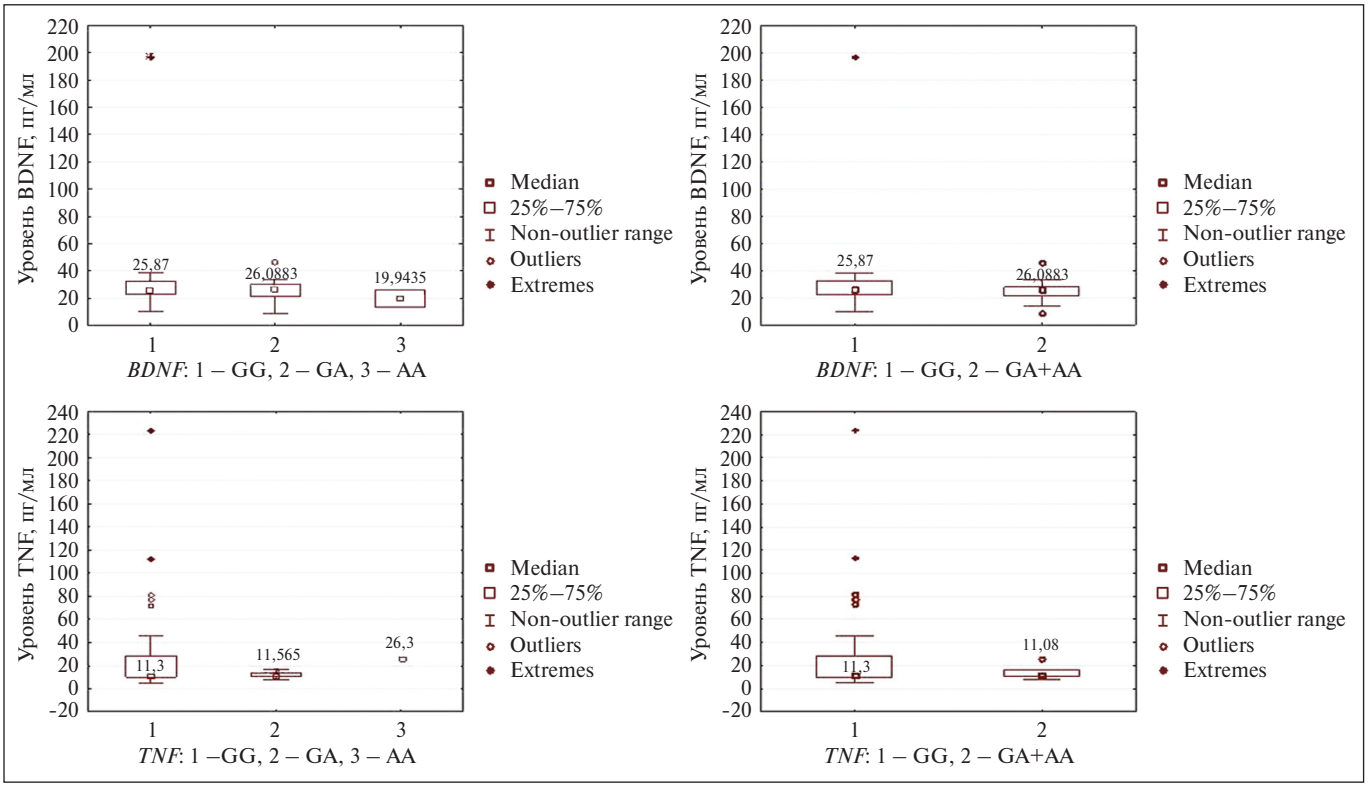

Fig. 2. *Influence of carriage of SNGs rs6265 of the BDNF gene and rs1800629 of the TNFA gene on the concentration of BDNF and TNFα in blood plasma*

When analyzing the concentration of BDNF and TNFα in blood plasma, depending on the rs6265 genotype of the *BDNF* gene and the rs1800629 genotype of the TNFA gene, no statistically significant differences were found (p>0.05; Fig. 2).

Discussion. TLE is the most common form of focal epilepsy in adults; in clinical practice patients with an unspecified etiological factor are the most common [1, 2].

In most cases, the causes of structural focal TLE are craniocerebral traumas, brain tumors, strokes, status epilepticus with the formation of HS [15–17]. In the course of TLE pharmacoresistance is typically formed. [16]. The proportion of patients achieving complete remission ranges from 11% to 25% (of whom 48% – with monotherapy and 52% – with polytherapy); the proportion of patients with a decrease (by 50% or more) in the frequency of seizures is 60%; and the proportion of those with absolute resistance is from 6% to 40 % [3, 18].

One of the priority areas now is research aimed at studying clinical diagnostic biomarkers of mesial TLE, particularly, in the context of its genetic, biochemical, neuroradiological, neurophysiological and clinical features.

The *IL-1β* (interleukin 1β) gene is localized in the q14 region of chromosome 2. The most interesting SNPs are located in the promoter region at the position IL-1β-511CT (rs16944), and in exon 5 of IL-1β-3953 CT (rs1143634) [19]. For IL-1β-511, a high frequency of the TT genotype was found in the group with mesial TLE with HS compared with the controls [20] and in a larger sample [21]. It was noted that the T rs16944 allele has a moderate effect on susceptibility to mesial TLE with HS [19]. According to the study by B. Leal et al. [22], the frequency of carriage of the TT rs16944 genotype was higher (p=0.021) in patients with mesial TLE with HS compared with the control group. However, these associations were not confirmed in other studies [23–27]. In our study, the carriage of SNP rs16944 and rs1143634 of the *IL-1β* gene did not show a statistically significant association with the development and course of TLE either.

The *BDNF* (brain-derived neurotrophic factor) gene is located in the p14.1 region of chromosome 11 [28]. One of the most studied SNP in the *BDNF* gene is the G/A nucleotide substitution at position 196 in exon 8 (rs6265), which leads to a decrease in the activity of BDNF-dependent secretion, significantly changing the intracellular transport and packaging of proBDNF [29, 30]. It has been shown that the rs6265 polymorphism of the *BDNF* gene may be associated with epileptogenesis, and the A allele plays a protective role in the development of epilepsy [31]. It was also found that the rs6265 polymorphism of the *BDNF* gene is associated with the development of epilepsy, especially in the Asian population [32]. Our study has found that the carriage of the GA rs6265 genotype of the *BDNF* gene is prognostically unfavorably associated with the development of TLE with HS, which is consistent with the studies of N. Shen et al. [31] and Xu Yue-Long et al. [32].

The *NTRK-2* gene of the neurotrophic tyrosine kinase receptor type 2 is a potential molecular target for blocking epileptogenesis and treating epilepsy [33]. Allelic variants of the *NTRK-2* gene initially were linked with depression and response to antidepressant therapy [34, 35], vulnerability to nicotine addiction [36], autism [37], and Alzheimer's disease [38].

There are few studies of *NTRK-2* gene variants in human epilepsy comparing the frequencies of *NTRK-2* gene variants between patients with mesial TLE and controls. The T rs3780645 allele was more common in patients receiving polytherapy than in those receiving monotherapy, which may indicate the difficulty of controlling seizures in this group of patients [39]. In our study, SNP rs3780645 of the *NTRK-2* gene did not show a statistically significant association with the development and the course of TLE.

In the present work, a statistically significant association of the carriage of the A allele and the GA rs1800629 genotype of the *TNFA* gene with the development of TLE was demonstrated for the first time. In addition, it was found that carriage of the genotype AA rs1800629 of the *TNFA* gene in patients with TLE has a protective effect and reduces the probability of AED polytherapy by 4.82 times (OR=4.82; 95% CI 1.71–13.61; p=0.003). On the other hand, in the study by B. Leal et al. [22] no association was found between the rs1800629 alleles and genotypes of the *TNFA* gene and susceptibility to mesial TLE with HS in 196 patients with TLE with HS compared with a control group from the Portuguese population.

According to the results of our study, there was no statistically significant correlation between the carriage of SNP rs6265 of the *BDNF* gene and rs1800629 of the *TNFA* gene and the concentration of BDNF and TNFα in blood plasma.

The lack of positive genetic associations with TLE, confirmed by several independent studies, may be due to the small sample size of patients with mesial TLE and/or clinical heterogeneity in almost all studies.

Conclusion. Based on the results of this work, we have established a prognostically unfavorable role of the carriage of the A allele and the GA rs1800629 genotype of the *TNFA* gene in the development of TLE, and the GA rs6265 genotype of the *BDNF* gene in the development of TLE with HS. Carrying the genotype AA rs1800629 of the *TNFA* gene in patients with TLE reduces the risk of AED polytherapy.

The analysis of the literature has shown that the study of the processes of neuroinflammation and neurodegeneration is important both from a physiological point of view and from the point of view of searching for markers of the development of TLE, which allow to predict and evaluate the rate of progression of the disease, to help determine the tactics of treatment and assess its effectiveness.

In this regard, identification of potential genetic markers currently remains an extremely urgent task.

REFERENCES

1. Карлов ВА. Эпилепсия у детей и взрослых женщин и мужчин: Руководство для врачей. 2-е изд. Москва: Бином; 2019. 893 с.
[Karlov VA. *Jepilepsija u detej i vzroslyh zhenshhin i muzhchin. Rukovodstvo dlja vrachej* [Epilepsy in children and adult women and men. Manual for physicians]. 2nd ed. Moskow: Binom; 2019. 893 p. (In Russ.)].

2. Tellez-Zenteno JF, Hernandez-Ronquillo L. A review of the epidemiology of temporal lobe epilepsy. *Epilepsy Res Treat.* 2012;2012:630853. doi: 10.1155/2012/630853. Epub 2011 Dec 29.

3. Одинак ММ, Базилевич СН, Прокудин МЮ и др. Фармакорезистентность при фокальных эпилепсиях у взрослых. В кн.: Гусева ЕИ, Гехт АБ, редакторы. Эпилепсия: фундаментальные, клинические и социальные аспекты. Москва: АПКИППРО; 2013. С. 691-701.
[Odinak MM, Bazilevich SN, Prokudin MYu, et al. Pharmacoresistance in focal epilepsy in adults. In: Guseva EI, Geht AB, editors. *Jepilepsija: fundamental'nye, klinicheskie i social'nye aspekty* [Epilepsy: fundamental, clinical and social aspects]. Moskow: APKIPPRO; 2013. P. 691-701 (In Russ.)].

4. De Lanerolle NC, Lee TS. New facets of the neuropathology and molecular profile of human temporal lobe epilepsy. *Epilepsy Behav.* 2005 Sep;7(2):190-203. doi: 10.1016/j.yebeh.2005.06.003

5. Panayotopoulos CP. The epilepsies: seizures, syndromes and management. Oxfordshire (UK): Bladon Medical Publishing; 2005. 540 p.

6. Липатова ЛВ, Серебряная НБ, Сивакова НА. Роль нейровоспаления в патогенезе эпилепсии. *Неврология, нейропсихиатрия, психосоматика.* 2018;10(1):38-45. doi: 10.14412/2074-2711-2018-1S-38-45
[Lipatova LV, Serebrjanaja NB, Sivakova NA. The role of neuroinflammation in the pathogenesis of epilepsy. *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics.* 2018;10(1):38-45. doi: 10.14412/2074-2711-2018-1S-38-45 (In Russ.)].

7. Vezzani A, Maroso M, Balosso S, et al. IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. *Brain Behav Immun.* 2011 Oct;25(7):1281-9. doi: 10.1016/j.bbi.2011.03.018. Epub 2011 Apr 5.

8. Vezzani A, Fujinami RS, White HS, et al. Infections, inflammation and epilepsy. *Acta Neuropathol.* 2016 Feb;131(2):211-34. doi: 10.1007/s00401-015-1481-5. Epub 2015 Sep 30.

9. Wahab A. Difficulties of treatment and management of epilepsy and challenges of new drug development. *Pharmaceuticals (Basel).* 2010 Jul 5;3(7):2090-110. doi: 10.3390/ph3072090

10. Ma L, Li R, Huang H, et al. Up-regulated BAFF and BAFF receptor expression in patients with intractable temporal lobe epilepsy and a pilocarpine-induced epilepsy rat model. *Seizure.* 2017 May;48:79-88. doi: 10.1016/j.seizure.2017.03.016. Epub 2017 Apr 8.

11. Yu N, Di Q, Hu Y, et al. A meta-analysis of pro-inflammatory cytokines in the plasma of epileptic patients with recent seizure. *Neurosci Lett.* 2012 Apr 11;514(1):110-5. doi: 10.1016/j.neulet.2012.02.070. Epub 2012 Mar 3.

12. Chen NC, Chuang YC, Huang CW, et al. Interictal serum brain-derived neurotrophic factor level reflects white matter integrity, epilepsy severity, and cognitive dysfunction in chronic temporal lobe epilepsy. *Epilepsy Behav.* 2016 Jun;59:147-54. doi: 10.1016/j.yebeh.2016.02.029. Epub 2016 May 3.

13. Thakran S, Guin D, Singh P, et al. Genetic Landscape of Common Epilepsies: Advancing towards Precision in Treatment. *Int J Mol Sci.* 2020 Oct 21;21(20):7784. doi: 10.3390/ijms21207784

14. Salzmann A, Malafosse A. Genetics of temporal lobe epilepsy: a review. *Epilepsy Res Treat.* 2012;2012:863702. doi: 10.1155/2012/863702. Epub 2012 Feb 19.

15. Котов АС, Рудакова ИГ, Котов СВ. Клиника, диагностика и лечение височной эпилепсии. *Эффективная фармакотерапия. Неврология и психиатрия.* 2010;(1):52-7.
[Kotov AS, Rudakova IG, Kotov SV. Clinic, diagnosis and treatment of temporal lobe epilepsy. *Jeffektivnaja farmakoterapija. Nevrologija i psihiatrija.* 2010;(1):52-7 (In Russ.)].

16. Мухин КЮ, Гатауллина СХ, Петрухин АС. Палеокортикальная височная

эпилепсия, обусловленная мезиальным височным склерозом: клиника, диагностика и лечение (обзор литературы). *Русский журнал детской неврологии*. 2008;(3):41-60. [Muhin KYu, Gataullina SKh, Petruhin AS. Paleocortical temporal lobe epilepsy due to mesial temporal sclerosis: clinic, diagnosis and treatment (literature review). *Russkij zhurnal detskoj nevrologii*. 2008;(3):41-60 (In Russ.)].

17. Шнайдер НА, Мартынова ГП, Строганова МА и др. Фебрильные приступы как триггер мезиального височного склероза: клинический случай. *Проблемы женского здоровья*. 2015;10(1):69-78. [Shnajder NA, Martynova GP, Stroganova MA, et al. Febrile seizures as trigger of mesial temporal sclerosis: case report. *Problemy zhenskogo zdorov'ja*. 2015;10(1):69-78 (In Russ.)].

18. Cendes F, Kanane P, Brodie M. Le syndrome d'epilepsiemesio-temporale. In: Roger J, Bureau M, Dravet, et al, editors. Les syndromes epileptiques de l'enfant et de l'adolescent. Montrouge: John Libbey; 2005. P. 555-67.

19. Kauffman MA, Moron DG, Consalvo D, et al. Association study between interleukin 1β gene and epileptic disorders: a HuGe review and meta-analysis. *Genet Med*. 2008 Feb;10(2):83-8. doi: 10.1097/GIM.0b013e318161317c

20. Kanemoto K, Kawasaki J, Miyamoto T, et al. Interleukin (IL)-1β, IL-1β, and IL-1 receptor antagonist gene polymorphisms in patients with temporal lobe epilepsy. *Ann Neurol*. 2000 May;47(5):571-4.

21. Kanemoto K, Kawasaki J, Yuasa S, et al. Increased frequency of interleukin-1β-511T allele in patients with temporal lobe epilepsy, hippocampal sclerosis, and prolonged febrile convulsion. *Epilepsia*. 2003 Jun;44(6):796-9. doi: 10.1046/j.1528-1157.2003.43302.x

22. Leal B, Chaves J, Carvalho C, et al. Immunogenetic predisposing factors for mesial temporal lobe epilepsy with hippocampal sclerosis. *Int J Neurosci*. 2018 Apr;128(4):305-10. doi: 10.1080/00207454.2017.1349122

23. Jin L, Jia Y, Zhang B, et al. Association analysis of a polymorphism of interleukin 1β (IL-1β) gene with temporal lobe epilepsy in a Chinese population. *Epilepsia*. 2003 Oct;44(10):1306-9. doi: 10.1046/j.1528-1157.2003.11003.x

24. Heils A, Haug K, Kunz WS, et al. Interleukin-1β gene polymorphism and susceptibility to temporal lobe epilepsy with hippocampal sclerosis. *Ann Neurol*. 2000 Dec;48(6):948-50.

25. Buono RJ, Ferraro TN, O'Connor MJ, et al. Lack of association between an interleukin 1 beta (IL-1β) gene variation and refractory temporal lobe epilepsy. *Epilepsia*. 2001 Jun;42(6):782-4. doi: 10.1046/j.1528-1157.2001.42900.x

26. Ozkara C, Uzan M, Tanriverdi T, et al. Lack of association between IL-1β/α gene polymorphisms and temporal lobe epilepsy with hippocampal sclerosis. *Seizure*. 2006 Jul;15(5):288-91. doi: 10.1016/j.seizure.2006.02.016

27. Yeni SN, Ozkara C, Buyru N, et al. Association between APOE polymorphisms and mesial temporal lobe epilepsy with hippocampal sclerosis. *Eur J Neurol*. 2005 Feb;12(2):103-7. doi: 10.1111/j.1468-1331.2004.00956.x

28. Yang W, Li J, Shang Y, et al. HMGB1-TLR4 axis plays a regulatory role in the pathogenesis of mesial temporal lobe epilepsy in immature rat model and children via the p38MAPK signaling pathway. *Neurochem Res*. 2017 Apr;42(4):1179-90. doi: 10.1007/s11064-016-2153-0

29. Martinez-Levy GA, Rocha L, Rodriguez-Pineda F, et al. Increased expression of Brain-Derived Neurotrophic Factor transcripts I and VI, cAMP response element binding, and glucocorticoid receptor in the cortex of patients with temporal lobe epilepsy. *Mol Neurobiol*. 2018 May;55(5):3698-708. doi: 10.1007/s12035-017-0597-0

30. Karnik MS, Wang L, Barch DM, et al. BDNF polymorphism rs6265 and hippocampal structure and memory performance in healthy control subjects. *Psychiatry Res*. 2010 Jul 30;178(2):425-9. doi: 10.1016/j.psychres.2009.09.008

31. Shen N, Zhu X, Lin H, et al. Role of BDNF Val66Met functional polymorphism in temporal lobe epilepsy. *Int J Neurosci*. 2016;126(5):436-41. doi: 10.3109/00207454.2015.1026967

32. Xu YL, Li XX, Zhuang SJ, et al. Significant association of BDNF rs6265 G>A polymorphism with susceptibility to epilepsy: a meta-analysis. *Neuropsychiatr Dis Treat*. 2018 Apr 16;14:1035-46. doi: 10.2147/NDT.S154927

33. Nakagawara A, Liu XG, Ikegaki N, et al. Cloning and chromosomal localization of the human TRK-B tyrosine kinase receptor gene (NTRK2). *Genomics*. 1995 Jan 20;25(2):538-46. doi: 10.1016/0888-7543(95)80055-q

34. Dong C, Wong ML, Licinio J. Sequence variations of ABCB1, SLC6A2, SLC6A3, SLC6A4, CREB1, CRHR1 and NTRK2: association with major depression and antidepressant response in Mexican-Americans. *Mol Psychiatry*. 2009 Dec;14(12):1105-18. doi: 10.1038/mp.2009.92

35. Hennings JM, Kohli MA, Czamara D, et al. Possible associations of NTRK2 polymorphisms with antidepressant treatment outcome: findings from an extended tag SNP approach. *PLoS One*. 2013 Jun 4;8(6):e64947. doi: 10.1371/journal.pone.0064947

36. Beuten J, Ma JZ, Payne TJ, et al. Association of specific haplotypes of neurotrophic tyrosine kinase receptor 2 gene (NTRK2) with vulnerability to nicotine dependence in African-Americans and European-Americans. *Biol Psychiatry*. 2007 Jan 1;61(1):48-55. doi: 10.1016/j.biopsych.2006.02.023

37. Correia CT, Coutinho AM, Sequeira AF, et al. Increased BDNF levels and NTRK2 gene association suggest a disruption of BDNF/TrkB signaling in autism. *Genes Brain Behav*. 2010 Oct;9(7):841-8. doi: 10.1111/j.1601-183X.2010.00627.x

38. Chen Z, Simmons MS, Perry RT, et al. Genetic association of neurotrophic tyrosine kinase receptor type 2 (NTRK2) With Alzheimer's disease. *Am J Med Genet B Neuropsychiatr Genet*. 2008 Apr 5;147(3):363-9. doi: 10.1002/ajmg.b.30607

39. Torres CM, Siebert M, Bock H, et al. NTRK2 (TrkB gene) variants and temporal lobe epilepsy: A genetic association study. *Epilepsy Res*. 2017 Nov;137:1-8. doi: 10.1016/j.eplepsyres.2017.08.010

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Panina Yu.S. http://orcid.org/0000-0001-5204-7482
Domoratskaya E.A. http://orcid.org/0000-0001-9946-2878
Dmitrenko D.V. http://orcid.org/0000-0003-4639-6365