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Роль полиморфизма гена *GRIN1* в формировании посттравматической эпилепсии

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АННОТАЦИЯ

Введение. В патогенезе припадков особая роль отводится NMDA-рецепторам, одна из субъединиц которых кодируется геном *GRIN1*. Известны мутации гена *GRIN1* у пациентов с различными формами эпилепсии и энцефалопатии. При этом, данные об участии *GRIN1* и его полиморфизмов в развитии посттравматической эпилепсии (ПТЭ) отсутствуют.

Цель. Определение влияния однонуклеотидного полиморфизма rs 1126442 гена *GRIN1* на риск формирования ПТЭ.

Материалы и методы. Обследовано 140 пациентов: 69 больных с ПТЭ, 71 пациент с генетической эпилепсией (ГЭ). Всем испытуемым проведено комплексное обследование с оценкой анамнеза, неврологического статуса, результатов электроэнцефалографии (ЭЭГ) и нейровизуализации, а также генотипирование образцов крови методом полимеразной цепной реакции в режиме реального времени. Контролем для генетического исследования явилась венозная кровь 60 здоровых лиц.

Результаты. У пациентов с ПТЭ преобладали фокальные приступы с переходом в билатеральные тонико-клонические. По данным нейровизуализации выявлялись дистрофические, кистозные и кистозно-глиозные изменения, признаки наружной гидроцефалии. При ЭЭГ регистрировалась интериктальная и иктальная эпилептиформная активность, а также тета-замедления. Генотипирование по полиморфизму rs 1126442 гена *GRIN1* выявило преобладание гетерозиготного генотипа G/A и гомозиготного A/A у пациентов с ПТЭ по кодоминантной (отношение шансов (ОШ) = 3,43; 95% доверительный интервал (ДИ): 1,56–7,55; p = 0,0047), доминантной (ОШ = 3,24; 95% ДИ: 1,57–6,68; p = 0,0011) и сверхдоминантной (ОШ = 2,90; 95% ДИ: 1,36–6,22; p = 0,0048) моделям наследования. Носительство гетерозиготного генотипа G/A rs 1126442 гена *GRIN1* ассоциировано с регистрацией эпилептиформной активности на ЭЭГ у всех пациентов, страдающих эпилепсией (ОШ = 2,40; 95% ДИ: 1,11–5,20; p = 0,024).

Заключение. Носительство гетерозиготного генотипа G/A и гомозиготного генотипа A/A rs 1126442 *GRIN1* по доминантной и кодоминантной моделям наследования ассоциировано с высоким риском развития эпилепсии после перенесенной черепно-мозговой травмы, а носительство гетерозиготного генотипа G/A rs 1126442 гена *GRIN1* ассоциировано с регистрацией эпилептиформной активности на ЭЭГ.

Ключевые слова: *черепно-мозговая травма; посттравматическая эпилепсия; генетическая эпилепсия; GRIN1*

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Role of the *GRIN1* gene polymorphism in the formation of post-traumatic epilepsy

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ABSTRACT

INTRODUCTION: NMDA receptors are involved in the pathogenesis of seizures, as it subunit is coded for by the *GRIN1* gene. Different *GRIN1* mutations are known in patients with different forms of epilepsy and encephalopathy. However, no data are available on the participation of the *GRIN1* gene and its polymorphisms in the development of post-traumatic epilepsy (PTE).

AIM: To determine the influence of single-nucleotide rs1126442 polymorphism of *GRIN1* on the risk of PTE formation.

MATERIALS AND METHODS: A total of 140 patients were examined, which included 69 patients with PTE and 71 patients with genetic epilepsy. All patients underwent a comprehensive examination, with evaluation of history, neurological status, electroencephalography (EEG) and neuroimaging results, and genotyping of blood samples by real-time polymerase chain reaction. The control sample for genetic examination was venous blood from 60 healthy individuals.

RESULTS: Focal seizures with transition to bilateral and tonic–clonic seizures were predominant in the PTE group. Neuroimaging revealed dystrophic, cystic, and cystogliotic alterations and signs of external hydrocephaly. EEG recorded interictal and ictal epileptiform activity and slowing of theta waves. Genotyping by rs1126442 polymorphism of *GRIN1* revealed predominance of heterozygous G/A and homozygous A/A genotypes in patients with PTE in the codominant (odds ratio (OD) = 3.43; 95% confidence index (CI) 1.56–7.55; p = 0.0047), dominant (OR = 3.24; 95% CI 1.57–6.68; p = 0.0011), and superdominant (OR = 2.90; 95% CI 1.36–6.22; p = 0.0048) inheritance models. The carriage of heterozygous G/A rs1126442 genotype of *GRIN1* was associated with an epileptiform activity in the EEG of all patients with epilepsy (OR = 2.40; 95% CI 1.11–5.20; p = 0.024).

CONCLUSION: The carriage of heterozygous G/A genotype and homozygous A/A rs 1126442 genotype of *GRIN1* in the dominant and codominant inheritance models is associated with a high risk of development of epilepsy after craniocerebral trauma. The carriage of heterozygous G/A rs 1126442 genotype of *GRIN1* is associated with an epileptiform activity in EEG.

Keywords: *craniocerebral trauma; post-traumatic epilepsy; genetic epilepsy; GRIN1*

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ECO•VECTOR

LIST OF ABBREVIATIONS

CCT – craniocerebral trauma
CI – confidence interval
CT – computed tomography
DNA – deoxyribonucleic acid
EDTA – ethylenediaminetetraacetic ethylene diamine tetracidic acid
EEG – electroencephalogram
GE – genetic epilepsy
GRIN1 – glutamate ionotropic receptor NMDA type subunit 1
GRIN2 – glutamate ionotropic receptor NMDA type subunit 2A
MRI – magnetic resonance imaging
NMDA – N-methyl-D-aspartate
OR – odds ratio
PCR – polymerase chain reaction
PTE – post-traumatic epilepsy

INTRODUCTION

The International League Against Epilepsy stated that "epilepsy is a chronic disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by neurobiological, cognitive, psychological and social consequences of this condition" [1]. Genetics was considered to play a role in the etiopathogenesis [2], and molecular genetic analyses have become increasingly performed, especially in the analysis of some genetic forms of epilepsy [2, 3]. One of the provoking epileptogenic factors is craniocerebral trauma (CCT), which results in the development of post-traumatic epilepsy (PTE) in 10%–30% of the cases [4, 5].

The pathogenetic mechanisms of epileptic seizures are attributed to N-methyl-D-aspartate (NMDA) receptors, whose subunits are encoded by glutamate ionotropic receptor NMDA type subunits 1 and 2 (*GRIN1* and *GRIN2* genes, respectively) [6–8]. *GRIN1* is located on the ninth chromosome, encodes the NR1 subunit of the glutamate receptor, and thus controls neuronal excitability and synaptic plasticity, which play a role in the pathogenesis of several neuropsychiatric diseases [6]. *GRIN1* is known to mutate in patients with early forms of hereditary epileptic encephalopathies, schizophrenia, and mental retardation [9, 10]. *GRIN1* is associated with a nervous system disorder known as *GRIN1*-NDD, which is manifested by mental retardation, epileptic seizures, and motor disorders [11]. According to some international authors [12, 13], *GRIN1* is associated with the early forms of epileptic encephalopathies and with hyperkinetic and stereotyped movements without accompanying epilepsy and psychoses. However, no evidence supports the participation of *GRIN1* and its polymorphisms in the structural development of PTE.

Aim — to determine the effect of rs1126442 mononucleotide polymorphism of *GRIN1* on the development of PTE.

MATERIALS AND METHODS

A simple one-stage (one visit) controlled randomized study was conducted. Clinical examination data, complaints, history, additional examination findings, and blood sampling for genetic analysis were analyzed. Before all procedures, each patient provided written consent, which reflects their awareness of and voluntary participation in the study. Genotyping was performed at the Laboratory of Immunogenetics of the Federal Scientific Center for Medical and Preventive Technologies of Public Health Risk Management (Perm).

The study was conducted in compliance with the international standards and bioethical norms, in accordance with the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" in 1964, taking into account the amendment of the 52nd session of the General Assembly in Edinburgh in 2000. The study protocol and informed consent form were approved by the Ethics Committee of Perm State Medical University after an expert assessment (Protocol of the meeting No. 4 of 24.04.19).

The study involved 140 patients aged 18–75 years (38 [27.0–48.0] years) who signed the informed consent. The main group was composed of patients with PTE (n = 69, aged 39 [21.0–52.0] years, 43 men), and the comparison group included patients with genetic epilepsy (GE, n = 71, aged 34 [19.0–41.0] years, 29 men). The control group included healthy individuals aged 35 [25.0–45.0] years (n = 61, 38 men).

The majority of the patients with PTE and GE presented with complaints of fear of seizures, headaches, and memory impairment. Undoubtedly, the development of the post-traumatic epileptogenic focus is attributed to structural alterations in the brain matter formed during the acute period of CCT in patients with PTE. Patients with a history of CCT often had epidural (n = 12) and subdural (n = 13) hematomas and intracerebral hematomas (n = 9), and there were single cases of penetrating wounds in the

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brain, crushing of the brain matter, and hygromas (n = 3). In the clinical picture, majority of the patients with PTE presented with focal seizures with transition to bilateral tonic–clonic (n = 52), less common bilateral tonic–clonic (n = 17), and focal (n = 7) seizures, which can be explained by the local characteristic of the epileptogenic focus.

In contrast to patients with PTE, isolated tonic–clonic seizures were predominant in those with GE (n = 53). Most patients diagnosed with PTE (n = 66) and GE (n = 51) had no hereditary burden for epilepsy. Thus, in patients with GE, heredity was a more common factor (n = 14) than in patients with PTE (n = 4).

In the neurological status assessment, neurological deficiency was not determined in 33 patients of the main group. However, 20 patients had motor disorders, such as hemiparesis and tetraparesis. Nine patients had impaired coordination of movements such as ataxic syndrome, two patients had speech disorders such as motor and sensorimotor aphasia, and one patient had signs of dysarthria. In the evaluation of the neurological status of patients with confirmed diagnoses of GE, no pathological neurological syndromes were found in most cases (n = 57). However, given the high frequency of epileptic seizures characterized by sudden falls with subsequent traumatization, two patients developed hemiparesis following CCT sustained due to bilateral tonic–clonic seizures.

Most patients with PTE (n = 66) and GE (n = 67) received antiepileptic therapy. However, three patients with PTE and four patients with GE refused anticonvulsive drugs, as they considered them ineffective. Patients with PTE and GE received monotherapy (n = 48 and n = 52, respectively). The following drugs were used: valproic acid, oxcarbazepine, carbamazepine, levetiracetam, topiramate, lamotrigine, clonazepam, and phenobarbital. In 18 patients with PTE and 15 with GE, dual agent therapy was used because of the ineffectiveness of monotherapy.

The location and type of morphological alterations of the brain were evaluated based on neuroimaging data in 31 patients with PTE and 57 with GE. Using magnetic resonance imaging (MRI) and computed tomography (CT) data, cortical atrophy was determined in 10 patients with PTE. Less common symptoms were cystic alterations (n = 3), signs of external hydrocephalus formed following atrophy (n = 5), dystrophic alterations (n = 4), cystogliotic alterations (n = 3), leukoaraiosis (n = 1), cerebellar atrophy (n = 1), hygroma (n = 1), and consequences of missile wounds (n = 1). In most patients with GE (n = 37), no structural alterations of the brain were determined, but the following cases were recorded: cystic alterations (n = 7), cortical atrophy (n = 3), signs of external hydrocephalus (n = 4), lateroventricular asymmetry (n = 2), and dystrophic alterations (n = 4).

Electroencephalography (EEG) was used to determine the focus of the epileptiform activity in the awake state. In patients with PTE, an epileptiform activity was recorded as sharp-slow wave complexes in the frontal–temporal leads (n = 2), parietal–occipital–temporal leads (n = 2), and left frontal–central leads (n = 5). In two patients, spike-and-wave complexes were detected in the parietal–temporal and frontal leads (n = 2). Epileptiform activity was also recorded in the frontal leads, combined with the phenomenon of secondary bilateral synchronization (n = 2). Moreover, EEG data revealed signs of organic alterations in the brain matter in the form of prolonged regional slow-wave activity in the theta range in the frontal (n = 10) and occipital (n = 1) leads. Diffuse slow-wave activity was observed in nine patients with PTE. In patients with GE, diffuse epileptiform activities in the form of sharp-and-slow wave (n = 6) and spike-and-wave (n = 6) complexes were recorded. Periodic regional slowdowns in the frontal–central leads were found in four patients. Patients with GE were more sensitive to photostimulation, in response to which generalized discharges in the form of spike-and-wave complexes were recorded. In patients with GE, typical patterns of absences were recorded as spike-and-wave complexes at 2.5–3 Hz per second and polyspike-and-wave complexes, indicating the presence of myoclonic seizures.

In all patients, comprehensive clinical examination was performed, including history and neurological status assessments based on routine methods. The results of instrumental methods of examination, such as EEG, CT, and MRI, were also evaluated. As biological sample, regardless of food intake, 5 mL of venous blood was collected into vacuum tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant for polymerase chain reaction (PCR). Prior to the examination, blood samples were kept at constant temperature of minus 18–20°C for 2–6 months. After defrosting before the PCR test, biological samples were prepared. For this, 100 μL of the analyzed blood sample and 300 μL of the lysing solution (0.5% solution of sarkozyl and 20 mg/mL proteinase in an acetate buffer with pH 7.5) were added into 1.5-mL test tubes (Eppendorf) for hemolysis of erythrocytes. Thereafter, sorbent (kaolin) was added, solutions were mixed on the vortex for 5 s, and droplets were precipitated by centrifugation at 1000 rpm. The samples were washed three times to remove the proteins and lipids by the removal of supernatants. Nucleic acids remained on the sorbent. Then, the adsorbed deoxyribonucleic acids (DNA) were extracted with TE buffer (a mixture of 10 mM tris-HCl and 1 mM EDTA, pH 8.0). The extract was subjected to centrifugation, and the resultant supernatant contained the purified DNA. DNA samples isolated from the blood samples were used for genotyping. PCR was performed on a detecting amplifier with hybridization-fluorescence detection in real time using ready-made sets of primers and probes (Thermo Fisher Scientific Applied Biosystems, USA), where DNA fragments of *GRIN1* (rs1126442) were used as primers.

Collected data were processed using Statistica 10 software package. For group comparison, nonparametric methods were used because they may be utilized in any quantitative and ordinal parameters and are resistant to high data variability, including those in small samples. For comparison of two independent samples of nonparametric data, Mann–Whitney U test was used.

Epilepsy-associated genotypes were analyzed using SNPstats program (Institut Català d'Oncologia, Spain). In the main analysis, odds ratio (OR) was used–a statistical parameter defined as a chance of the presence of an effect in the main group divided by the chance of an effect in the control group (used with 95% confidence interval (CI)). The critical level of significance in the verification of statistical hypotheses was set at 0.05.

RESULTS

The genetic study showed the following distribution of the rs1126442 polymorphism genotypes of *GRN1* among patients with PTE.

The frequency of occurrence of variant genotype A/A was 13%; heterozygous genotype G/A, 46%; and homozygous genotype G/G, 41%. In patients with GE, the heterozygous genotype G/A was predominant, with 48%; variant genotype A/A, 10%; homozygous genotype G/G, 42%, of the rs1126442 polymorphism of *GRIN1*. In the control group, the homozygous genotype G/G of the rs1126442 polymorphism of *GRIN1* was predominant (69%), the heterozygous genotype G/A was noted in 23%, and the variant A/A genotype was recorded in 8% of the cases.

To identify the association of carriage of the polymorphism genotypes of *GRIN1* with the risk of PTE and GE development, associations were analyzed using SNPstats software. Among patients with PTE, the heterozygous G/A and homozygous A/A genotypes of the rs1126442 polymorphism of *GRIN1* were reliably more common in the codominant (OR = 3.43; 95% CI 1.56–7.55; p = 0.0047), dominant (OR = 3.24; 95% CI 1.57–6.68; p = 0.0011), and superdominant (OR = 2.90; 95% CI 1.36–6.22; p = 0.0048) inheritance modes (Table 1).

Table 1. Association of the carriage of the rs1126442 polymorphism genotypes of *GRIN1* with post-traumatic epilepsy

Inheritance mode	Genotype	Main group, post-traumatic epilepsy, n (%)	Control group, n (%)	OR (95% CI)	p
Codominant	G/G	28 (40.6)	42 (68.8)	1.00	**0.0047**
	G/A	32 (46.4)	14 (22.9)	**3.43 (1.56–7.55)**	
	A/A	9 (13.0)	5 (8.2)	2.70 (0.82–8.90)	
Dominant	G/G	28 (40.6)	42 (68.8)	1.00	**0.0011**
	G/A-A/A	41 (59.4)	19 (31.1)	**3.24 (1.57–6.68)**	
Recessive	G/G-G/A	60 (87.0)	56 (91.8)	1.00	0.5700
	A/A	9 (13.0)	5 (8.2)	1.68 (0.53–5.32)	
Superdominant	G/G-A/A	37 (3.6)	47 (77.0)	1.00	**0.0048**
	G/A	32 (46.4)	14 (22.9)	**2.90 (1.36–6.22)**	

Note: OD — odds ratio; CI — confidence interval

Among patients with GE, the heterozygous G/A genotype of the rs1126442 polymophism of *GRIN1* was predominant in the codominant (OR = 0.29; 95% CI 0.13–0.64; p = 0.0062), dominant (OR = 0.33; 95% CI 0.16–0.68; p = 0.002), and superdominant (OR = 0.32; 95% CI 0.15–0.69; p = 0.0027) inheritance modes (Table 2).

As shown in Table 3, no reliable differences were found in the genotype frequencies of the rs1126442 polymorphism of *GRIN1* between patients with PTE and GE (p > 0.05).

Thus, the carriage of the heterozygous G/A rs1126442 genotype and homozygous A/A rs1126442 genotype of *GRIN1* in patients with PTE and the heterozygous G/A rs1126442 genotype of *GRIN1* in patients with GE shows the predisposition to the development of epilepsy.

In patients with PTE and GE, no associations were found between the rs1126442 genotypes of *GRIN1* with the type of epileptic seizures (Table 4).

In all patients with epilepsy (PTE and GE) carrying the heterozygous G/A rs1126442 genotype of *GRIN1*, using the superdominant (OR = 2.40; 95% CI 1.11–5.20; p = 0.024) inheritance models, the epileptiform activity on the EEG was reliably more common as shown in Table 5. In a comparative analysis of patients with PTE and GE by this criterion, no reliable differences were found (p = 0.097).

The rs1126442 polymorphism of *GRIN1* was not associated with tolerance to antiepileptic drugs (p = 0.8) and hereditary burden (p = 0.49).

Table 2. Association of the carriage of the rs1126442 polymorphism genotypes of GRIN1 with genetic epilepsy

Inheritance mode	Genotype	Main group, genetic epilepsy, n (%)	Control group, n (%)	OR (95% CI)	p
Codominant	G/G	30 (42.2)	42 (68.8)	1.00	**0,0062**
	G/A	34 (47.9)	14 (22.9)	**0.29 (0.13–0.64)**	
	A/A	7 (9.9)	5 (8.2)	0.51 (0.15–1.76)	
Dominant	G/G	30 (42.2)	42 (68.8)	1.00	**0,0020**
	G/A-A/A	41 (57.8)	19 (31.1)	**0.33 (0.16–0.68)**	
Recessive	G/G-G/A	64 (90.5)	56 (91.8)	1.00	0,7400
	A/A	7 (9.9)	5 (8.2)	0.82 (0.25–2.72)	
Superdominant	G/G-A/A	37 (52.1)	47 (77.0)	1.00	**0,0027**
	G/A	34 (47.9)	14 (22.9)	**0.32 (0.15–0.69)**	

Note: OD — odds ratio; CI — confidence interval

Table 3. Comparative analysis of the frequency of rs1126442 polymorphism genotypes of GRIN1 in patients with post-traumatic and genetic epilepsy

Inheritance mode	Genotype	Genetic epilepsy, n (%)	Post-traumatic epilepsy, n (%)	OR (95% CI)	p
Codominant	G/G	30 (42.2)	28 (40.6)	1.00	0.840
	G/A	34 (47.9)	32 (46.4)	1.01 (0.50–2.04)	
	A/A	7 (9.9)	9 (13.0)	1.38 (0.45–4.20)	
Dominant	G/G	30 (42.2)	28 (40.6)	1.00	0.840
	G/A-A/A	41 (57.8)	41 (59.4)	1.07 (0.55–2.10)	
Recessive	G/G-G/A	64 (90.1)	61 (87.0)	1.00	0.550
	A/A	7 (9.9)	9 (13.0)	1.37 (0.48–3.91)	
Superdominant	G/G-A/A	37 (52.1)	37 (53.6)	1.00	0.860
	G/A	34 (47.9)	32 (46.4)	0.94 (0.48–1.83)	

Note: OD — odds ratio; CI — confidence interval

Table 4. Association of the rs1126442 polymorphism genotypes of *GRIN1* with the types of seizures in patients with post-traumatic and genetic epilepsy

Inheritance mode	Genotype	Focal + bilateral tonic–clonic seizures, n (%)	Bilateral tonic–clonic seizures, n (%)	OR (95% CI)	p
Codominant	G/G	22 (36.7)	36 (45.0)	1.00	0.190
	G/A	32 (53.3)	34 (42.5)	2.05 (0.80–5.27)	
	A/A	6 (10.0)	10 (12.5)	0.72 (0.18–2.92)	
Dominant	G/G	22 (36.7)	36 (45.0)	1.00	0.270
	C/A-A/A	38 (63.3)	44 (55.0)	1.63 (0.68–3.92)	
Recessive	G/G-G/A	54 (90.0)	70 (87.5)	1.00	0.300
	A/A	6 (10.0)	10 (12.5)	0.50 (0.13–1.86)	
Superdominant	G/G-A/A	28 (46.7)	46 (57.5)	1.00	0.076
	G/A	32 (53.3)	34 (42.5)	2.20 (0.90–5.38)	

Note: OD — odds ratio; CI — confidence interval

Table 5. Associations of the rs1126442 polymorphism genotypes of *GRIN1* with the interictal activity in patients with post-traumatic and genetic epilepsy based on encephalogram data

Inheritance mode	Genotype	Epiactivity absent, n (%)	Epiactivity present, n (%)	OR (95% CI)	p
Codominant	G/G	29 (46.8)	18 (32.7)	1.00	0.075
	G/A	25 (40.3)	33 (60.0)	2.32 (1.03–5.25)	
	A/A	8 (12.9)	4 (7.3)	0.84 (0.21–3.33)	
Dominant	G/G	29 (46.8)	18 (32.7)	1.00	0.089
	C/A-A/A	33 (53.2)	37 (67.3)	1.95 (0.90–4.26)	
Recessive	G/G-G/A	54 (87.1)	51 (92.7)	1.00	0.320
	A/A	8 (12.9)	4 (7.3)	0.53 (0.14–1.92)	
Superdominant	G/G-A/A	3 (59.7)	22 (40.0)	1.00	**0.024**
	G/A	25 (40.3)	33 (60.0)	**2.40 (1.11–5.20)**	

Note: OD — odds ratio; CI — confidence interval

DISCUSSION

Considering the high incidence of CCT in individuals of working age, the prediction of the consequences of cerebral damage, particularly the probabilities for the development of epilepsy, should be investigated. In this context, the problem of searching for objective genetic markers becomes important. The results of this study *revealed the predomination of the heterozygous G/A rs1126442 genotype of GRIN1 in patients with PTE and GE* (in the codominant, dominant, and superdominant modes of inheritance) with no reliable differences in the genotype frequency between the two disease forms. In addition, epileptic activity was significantly more often recorded in the EEG of patients of the main and control groups who were carriers of the G/A rs1126442 genotype of *GRIN1*. This finding suggest the *participation of the studied polymorphism in the pathogenesis of epilepsy irrespective of the etiological factor, and the presence of the G/A rs1126442 genotype of GRIN1 can be reasonably used as a marker of potential predisposition to epilepsy*.

Thus, the proposed phenotyping method can be used as an additional (prognostic) criterion of the development of PTE in patients with a history of CCT (also in the early period for the determination of treatment tactics), and we have registered this method as an intellectual product [14].

CONCLUSION

Genotyping for the rs1126442 polymorphism of *GRIN1* revealed an association of the heterozygous G/A genotype with the risk of the development of epilepsy in patients with a history of CCT with dominant and codominant modes of inheritance. With this, the mentioned genotypes were not associated with the clinical manifestations of epilepsy and tolerance to anticonvulsants.

An association was established between the carriage of the heterozygous G/A genotype of the rs1126442 polymorphism of *GRIN1* with the epileptiform activity in the EEG of patients with PTE and GE.

ADDITIONAL INFORMATION

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