УДК 616.895.8:613.84:613.816:575.174.015.3
https://doi.org/10.20538/1682-0363-2022-3-105-111

Association of polymorphic variants of *GRIN2A* and *GRIN2B* genes with alcohol and tobacco abuse in patients with schizophrenia

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ABSTRACT

Aim. To compare the frequency of genotypes for polymorphic variants of *GRIN2A* and *GRIN2B* genes in patients with schizophrenia and addictive behavior (alcohol / tobacco abuse) and in patients with schizophrenia without addictive behavior in the Slavic population of the Tomsk region.

Materials and methods. The study included 219 inpatients with the established diagnosis of schizophrenia who received treatment in the clinics of Mental Health Research Institute and Tomsk Clinical Psychiatric Hospital. A history of alcohol / tobacco abuse was identified during a clinical interview and objective data collection. DNA was isolated from peripheral blood leukocytes by standard phenol – chloroform extraction.

15 single nucleotide polymorphisms (SNPs) in the *GRIN2A* gene and 9 polymorphisms in the *GRIN2B* gene were selected for genotyping. Allelic variants were determined by real-time polymerase chain reaction (PCR) with specific primers. The SPSS 17.0 software package was used for statistical data processing. The distribution of genotype frequency was assessed using the Pearson's $\chi 2$ test with the Yates' correction and the Fisher's exact test.

Results. Significant differences in the allele frequency for the rs9788936 polymorphism in the *GRIN2A* gene ($\chi 2 = 4.23$, $p = 0.04$) and for the rs10845838 polymorphism in the *GRIN2B* gene ($\chi 2 = 4.27$, $p = 0.04$) were revealed between the groups of patients with and without alcohol abuse. It was found that the polymorphic variant rs8049651 of the *GRIN2A* gene had a clear association ($F = 8.06$, $p = 0.029$) with the development of tobacco addiction in patients with schizophrenia.

Conclusion. The study identified the association between alcohol abuse and the rs9788936 polymorphism in the *GRIN2A* gene and the rs10845838 polymorphism in the *GRIN2B* gene in patients with schizophrenia. The association between the rs8049651 and rs7190619 polymorphisms in the *GRIN2A* gene and the development of tobacco abuse in patients with schizophrenia was revealed.

Keywords: schizophrenia, genetics, single nucleotide polymorphisms, smoking, alcohol addiction, glutamate

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

Source of financing. The study was supported by the Russian Science Foundation grant No. 21-15-00212 "The role of DNA methylation and gene polymorphism of the glutamatergic system in clinical practice, cognitive deficit, and schizophrenia therapy", 2021–2023.

Conformity with the principles of ethics. All patients included in the treatment and control groups signed an informed consent to participate in the study. The study was approved by the Ethics Committee at the Mental Health Research Institute, Tomsk NRMC (Protocol No. 142 of 14.05.2021).

For citation: Tiguntsev V.V., Gerasimova V.I., Kornetova E.G., Fedorenko O.Y., Semke A.V., Kornetov A.N. Association of polymorphic variants of *GRIN2A* and *GRIN2B* genes with alcohol and tobacco abuse in patients

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with schizophrenia. *Bulletin of Siberian Medicine.* 2022;21(3):105–111. https://doi.org/10.20538/1682-0363-2022-3-105-111.

Ассоциации полиморфных вариантов генов *GRIN2A* и *GRIN2B* со злоупотреблением алкоголем и табаком у больных шизофренией

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РЕЗЮМЕ

Цель. Сравнить частоты генотипов полиморфных вариантов генов *GRIN2A* и *GRIN2B* в группах больных шизофренией с аддиктивным поведением (злоупотребление алкоголем и курение табака) и без них в славянской популяции Томской области.

Материалы и методы. Обследованы 219 пациентов с установленным диагнозом «шизофрения», проходивших стационарное лечение в клиниках НИИ психического здоровья Томского НИМЦ и Томской клинической психиатрической больницы. Наличие злоупотребления алкоголем и курения в анамнезе выявлялось в процессе клинического интервью и сбора объективных сведений. ДНК выделяли из лейкоцитов периферической крови стандартным фенол-хлороформным методом.

Для генотипирования было выбрано 15 SNP в гене *GRIN2A* и 9 полиморфизмов в гене *GRIN2B*. Определение аллельных вариантов проводили методом real-time PCR со специфическими праймерами. Для статистической обработки данных использовался пакет программ SPSS 17.0. Распределение частот генотипов оценивалось при помощи критерия χ2 Пирсона с поправкой Йетса и точного теста Фишера.

Результаты. Выявлены статистически значимые различия в частотах аллелей полиморфизма rs9788936 в гене *GRIN2A* ($\chi^2 = 4{,}23$; $p = 0{,}04$), а также полиморфного варианта rs10845838 в гене *GRIN2B* ($\chi^2 = 4{,}27$; $p = 0{,}04$) в группах пациентов, злоупотребляющих алкоголем, и непьющих. Было установлено, что полиморфный вариант rs8049651 гена *GRIN2A* имеет четкую ассоциацию ($F = 8{,}06$; $p = 0{,}029$) с формированием зависимости от табака у больных шизофренией.

Заключение. Показаны ассоциации злоупотребления алкоголем с полиморфным вариантом rs9788936 в гене *GRIN2A* и полиморфным вариантом rs10845838 в гене *GRIN2B* у пациентов с шизофренией, а также ассоциация полиморфных вариантов rs8049651 и rs7190619 гена *GRIN2A* с формированием табачной зависимости у больных шизофренией.

Ключевые слова: шизофрения, генетика, однонуклеотидные полиморфизмы, курение, алкоголизм, глутамат

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование выполнено за счет гранта РНФ № 21-15-00212 «Роль метилирования ДНК и полиморфизма генов глутаматергической системы в клинике, когнитивном дефиците и терапии шизофрении», 2021–2023 гг.

Соответствие принципам этики. Все лица, входившие в основную и контрольную группы, дали информированное согласие на участие в исследовании. Исследование одобрено этическим комитетом НИИ психического здоровья Томского НИМЦ (протокол № 142 от 14.05.2021).

Для цитирования: Тигунцев В.В., Герасимова В.И., Корнетова Е.Г., Федоренко О.Ю., Семке А.В., Корнетов А.Н. Ассоциации полиморфных вариантов генов grin2a и grin2b со злоупотреблением алкоголем и табаком у больных шизофренией. *Бюллетень сибирской медицины.* 2022;21(3):105–111. https://doi.org/10.20538/1682-0363-2022-3-105-111.

INTRODUCTION

Psychoactive substance abuse is quite common in patients with schizophrenia. Thus, the risk of developing mental disorders associated with alcohol abuse in this cohort is three times higher than in the general population [1]. A recent meta-analysis showed that the lifetime prevalence of alcohol-related disorders in this group of patients is 24.3% [2]. Symptoms of alcohol abuse are often present before the onset of a psychotic disorder [3]. It does not matter which of these disorders manifests earlier, as their comorbidity is characterized by poor prognosis, increased risk of relapses, and instability of remissions [4]. In individuals with schizophrenia, alcohol abuse is associated with depression, a high risk of suicide, poor adherence to antipsychotic medications, chronic physical illness, homelessness, high levels of aggression, and frequent hospitalizations [5]. Alcohol abuse in patients with schizophrenia often contributes to the development of a hostile attribution bias, which is closely associated with delusions, delusional thinking, and the ability to recognize emotions [6].

Currently, there are a number of theories that attempt to explain high comorbidity of schizophrenia and alcohol abuse. First of all, this is the diathesis – stress model proposed in 1970 to describe the contribution of predisposed vulnerability and life experiences to the development of the disorder [7]. The alternative is the self-medication hypothesis, which suggests that individuals with schizophrenia use psychoactive substances to relieve symptoms or as an attempt to reduce adverse events of antipsychotic treatment. However, the latter has not been confirmed by research; among young people with a first episode psychosis, substance use disorder often developed before treatment [8]. There is also a unifying hypothesis that comorbidity of schizophrenia and substance abuse may be associated with dysregulation of the reward pathway in the brain (primary addiction hypothesis or reward deficiency syndrome), which was studied using functional magnetic resonance imaging (fMRI) [9].

The idea that early brain development disruption may lead to the onset of schizophrenia in late adolescence or early adulthood is one of the most promising theories. It is notable that in animal models of schizophrenia (based on neonatal ventral hippocampal damage), experimental rats consumed more psychoactive substances than the control group [10]. These data indicate a high probability of a common biological and, possibly, genetic substrate in schizophrenia and alcohol-related disorders.

The prevalence of tobacco smoking among patients with schizophrenia is 2–3 times higher than in the general population in Western countries [11]. Recent epidemiological, biological, and clinical data indicate a correlation between smoking, severity of positive symptoms, and the frequency of suicidal tendencies in patients with schizophrenia [12].

Some studies show that there are also common pathogenetic pathways in schizophrenia and tobacco addiction. A group of authors led by S. Leonard [13] found that various polymorphic patterns in the promoter region of the nicotinic acetylcholine receptor α7-subunit gene (*CHRNA7* or α7), leading to a decrease in the transcription of this gene, are significantly more frequent in patients with schizophrenia compared with healthy individuals.

It was established that negative symptoms of schizophrenia are associated with NMDA receptor hypofunction [14]. Exposure to nicotine during systematic tobacco smoking increases the density of NMDA receptors in the hippocampus and at the same time enhances glutamatergic activity through the activation of presynaptic nicotinic acetylcholine receptors [15]. It leads to stimulation of the release and metabolism of dopamine, one of the fundamental neurotransmitters in the pathogenesis of schizophrenia. Also, nicotinic acetylcholine receptors modulate activity in the frontal and parietal lobes of the cerebral hemispheres, thereby participating in excitation and motor activity, as well as in glutamatergic neurotransmission [16, 17].

Glutamate is the main excitatory neurotransmitter of the neocortex [18]. The imbalance between glutamate and its metabolite, the inhibitory neurotransmitter GABA, is involved in the pathogenesis of a number of mental and neurodegenerative diseases [19, 20]. The main physiological function of glutamate is participation in the intracellular regulation of Ca^{2+} ions. Accumulation of glutamate in the extracellular space and, as a result, entry of high levels of calcium ions into the cell through NMDA receptors underlie the phenomenon of excitotoxicity [21].

Glutamatergic activity plays a role in brain development, synaptic plasticity, mood disorders, and schizophrenia spectrum disorders [22, 23]. Proteins encoded by the *GRIN2A* and *GRIN2B* genes are subunits of the NMDA receptor, a member of the ionotropic glutamate receptor superfamily. The GRIN2B protein also acts as a receptor agonist binding site. In turn, NMDA receptors are involved in the calcium-mediated component of excitatory synaptic transmission in the central nervous system.

Based on these data, we have formulated a hypothesis that polymorphic variants of the *GRIN2A* and *GRIN2B* genes may be associated with the development of addictive behavior in patients with schizophrenia.

The aim of this study was to compare the frequency of genotypes for polymorphic variants of *GRIN2A* and *GRIN2B* genes in patients with schizophrenia with comorbid addictive behavior (alcohol abuse and tobacco use) and in patients with schizophrenia without addictive behavior in the Slavic population of the Tomsk region.

MATERIALS AND METHODS

The study involved 219 patients with an established diagnosis of schizophrenia who received inpatient treatment at the clinics of the Mental Health Research Institute of Tomsk NRMC and in the Tomsk Regional Psychiatric Hospital. Alcohol abuse and smoking history were identified during a clinical interview and objective data collection.

The study was carried out in accordance with ethical standards of the Declaration of Helsinki developed by the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects" as amended in 2000 and the "Rules of Clinical Practice in the Russian Federation" approved by Order of the Ministry of Healthcare of the Russian Federation No. 266 of 19.06.2003. The main inclusion criteria for patients were a verified diagnosis of schizophrenia according to ICD-10 (International Classification of Diseases, Tenth Revision), age 18–65 years, a signed informed consent from the patient, Caucasian race, and permanent residence in Western Siberia. Exclusion criteria were acute and chronic infectious, inflammatory, autoimmune, and somatic symptom diseases in the acute phase, as well as dependence on opioids, cannabis, sedatives, hypnotics, cocaine, and other stimulants, including caffeine, hallucinogens, and inhalants.

The sample size was 219 people: 144 men (65.8%) and 75 women (34.2%). The study included persons aged 18–65 years, the average age was 38.9 ± 13.4 years.

The majority of the examined patients – 114 (52.1%) – had disease duration of more than 10 years. The disorder duration of 5–10 years was observed in 44 patients (20.1%), duration of 1–5 years – in 47 patients (21.5%), and less than 1 year – in 8 patients (3.7%). The age of disease onset and duration could not be established in three people. The duration of alcohol and tobacco abuse corresponded to that of the disease.

Daily chlorpromazine equivalent (CPZeq) dose of all antipsychotics was 536 [240; 762.5] mg; the median duration of treatment was 11 [4; 21] years. During the initial examination of patients using the PANSS, we obtained the following results (Table 1).

Table 1

PANSS parameters in patients of the sample

Scale	*n*	*Me* [Q_1; Q_3]
Positive symptoms	219	21 [18; 26]
Negative symptoms	219	26 [22; 31]
General psychopathological symptoms	219	52 [42; 63]
Total	219	99 [85; 118]

DNA was isolated from peripheral blood leukocytes using standard phenol – chloroform extraction. A total of 15 single nucleotide polymorphisms (SNPs) in the *GRIN2A* gene and 9 SNPs in the *GRIN2B* gene were selected for genotyping. Allelic variants were determined by real-time PCR with specific primers using the SNP Genotyping Assay kits on StepOnePlus real-time PCR system (USA). SPSS 17.0 software was used for statistical data processing. Genotype frequency distribution was assessed using the Pearson's $\chi 2$ test with the Yates's correction and the Fisher's exact test (*F*).

RESULTS

Statistically significant differences were found in the allele frequency of the rs9788936 polymorphism in the *GRIN2A* gene ($\chi^2 = 4.23$; $p = 0.04$) and the rs10845838 polymorphism in the *GRIN2B* gene ($\chi^2 = 4.27$; $p = 0.04$) in the group of patients with comorbid alcohol abuse and in the group of patients without alcohol abuse (Table 2). The G allele of the rs9788936 polymorphism (odds ratio (OR) = 0.47; 95% confidence interval (CI): 0.22–0.98) and the A allele of the rs10845838 polymorphism (OR = 0.60; 95% CI: 0.37–0.98) have a protective effect. At the same time, the A allele of the rs9788936 polymorphism (OR = 2.15; 95% CI: 1.02–4.51) and the G allele of the rs10845838 polymorphism (OR = 1.64; 95% CI: 1.02–2.72) predispose to alcohol abuse.

It was also found that the rs8049651 polymorphic variant of the *GRIN2A* gene had a clear association ($F = 8.06$; $p = 0.029$) with tobacco addiction development in patients with schizophrenia (Table 3). In terms of statistical significance, the AG genotype was less common in the group of smokers (OR = 0.48; 95%

CI: 0.26–0.87) compared with the group of non-smokers. Also, the analysis of the allele distribution showed that their frequencies in the rs7190619 polymorphic variant of the *GRIN2A* gene were significantly different in the groups of smokers and non-smokers ($\chi^2 = 4.71$; $p = 0.03$). The OR for the A allele was 0.49 [95% CI: 0.25–0.94], for the G allele it was 2.05 [95% CI: 1.06–3.94].

Table 2

Frequency distribution for genotypes and alleles of *GRIN2A* and *GRIN2B* gene polymorphisms in persons with schizophrenia with alcohol abuse and in persons with schizophrenia without alcohol abuse, abs., %

SNP	Genotypes / Alleles	Alcohol abuse	No alcohol abuse	OR	95% CI	*F*/χ2	*p*
GRIN2A							
rs9788936	AA	34 (79.1%)	102 (63.0%)	0.45	0.20–1.00	*F* = 4.32	0.18
	AG	9 (20.9%)	55 (34.0%)	1.94	0.87–4.34		
	GG	0 (0%)	5 (3.0%)	–	–		
	A	77 (89.5%)	259 (79.9%)	2.15	1.02–4.51	$\chi^2 = 4.23$	0.04*
	G	9 (10.5%)	65 (20.1%)	0.47	0.22–0.98		
rs11866328	AA	4 (9.3%)	19 (11.4%)	1.26	0.41–3.92	*F* = 0.12	0.969
	AC	15 (34.9%)	90 (54.2%)	2.21	1.10–4.44		
	CC	24 (55.8%)	57 (34.3%)	0.41	0.21–0.82		
	A	23 (26.7%)	128 (38.6%)	0.58	0.34–0.99	$\chi^2 = 28.9$	< 0.001*
	C	63 (73.3%)	204 (61.4%)	1.72	1.02–2.91		
GRIN2B							
rs10845838	AA	8 (19.0 %)	19 (11.7%)	0.56	0.23–1.39	$\chi^2 = 4.3$	0.12
	AG	22 (52.4%)	70 (42.9%)	0.68	0.35–1.35		
	GG	12 (28.6%)	74 (45.4%)	2.08	0.99–4.34		
	A	38 (45.2%)	108 (33.5%)	1.64	1.005–2.67	$\chi^2 = 4.27$	0.04*
	G	46 (55.8%)	214 (66.5%)	0.61	0.38–0.995		

* p value < 0.05 (here and in Table 3).

Table 3

SNP	Genotypes / Alleles	Smokers	Non-smokers	OR	95% CI	*F*/χ2	*p*
rs7190619	AA	0 (0%)	3 (6.0%)	–	–	*F* = 7.29	0.051
	AG	25 (19.4%)	12 (24.0%)	0.76	0.35–1.66		
	GG	104 (70.6%)	35 (70.6%)	1.78	0.85–3.76		
	A	25 (9.7%)	18 (18.0%)	0.49	0.25–0.94	$\chi^2 = 4.71$	0.03*
	G	233 (90.3%)	82 (82.0%)	2.05	1.06–3.94		
rs8049651	AA	19 (12.2%)	4 (6.7%)	1.94	0.63–5.96	*F* = 8.06	0.029*
	AG	65 (41.7%)	36 (60.0%)	0.48	0.26–0.87		
	GG	72 (46.1%)	20 (33.3%)	1.71	0.92–3.19		
	A	103 (33.0%)	44 (36.7%)	0.85	0.55–1.32	$\chi^2 = 0.52$	0.47
	G	209 (67.0%)	76 (64.3%)	1.18	0.76–1.82		

DISCUSSION

In this study, we analyzed the associations of alcohol and tobacco abuse with 17 polymorphic variants of two genes involved in glutamate metabolism. The results led to the conclusion that two polymorphisms (rs8049651 and rs7190619) in the *GRIN2A* gene contribute to the development of tobacco addiction in patients with schizophrenia. Polymorphic variants rs9788936 and rs11866328 of the *GRIN2A* gene and rs10845838 of the *GRIN2B* gene demonstrated a strong association with alcohol abuse in both groups. In addition, the rs2072450 polymorphism in the *GRIN2A* gene may be associated with disruptions in aversion learning, and its allelic state may be one of the risk factors for alcohol addiction development [24].

The rs2058878 and rs2300272 polymorphisms of the *GRIN2B* gene may serve as an indicator of the ef-

fectiveness of acamprosate in the treatment of alcohol-related disorders [25], since researchers demonstrated an association of allelic variants of these polymorphisms with the duration of alcohol abstinence in patients.

The role of heredity in the pathogenesis and clinical presentation of schizophrenia is undeniable, and the associations we found also reflect this association. The influence of genetic factors and glutamatergic neurotransmission on the development of pathological behavioral patterns in patients with schizophrenia is a poorly studied issue in modern biological psychiatry.

The majority of genetic studies on schizophrenia are associated with its key symptoms (positive, negative, and cognitive), while a few works dedicated to comorbidity of schizophrenia and addictive disorders cannot fully cover the issue yet. Further research in this area, combining both genetic and clinical approaches, may define the role of glutamate in the development of addictive behavior in patients with schizophrenia.

CONCLUSION

This study showed associations of alcohol abuse with the rs9788936 polymorphic variant in the *GRIN2A* gene and the rs10845838 polymorphic variant in the *GRIN2B* gene in patients with schizophrenia. The study also demonstrated that rs8049651 and rs7190619 polymorphic variants of the *GRIN2A* gene have a clear association with the development of tobacco addiction in patients with schizophrenia.

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Tiguntsev V.V. – collection of clinical and biological material, analysis and interpretation of the data, drafting of the manuscript. Gerasimova V.I. – collection of clinical material, drafting of the manuscript. Kornetova E.G. – conception and design, drafting of the manuscript, final approval of the manuscript for publication. Fedorenko O.Yu. – conception and design. Semke A.V. – substantiation of the manuscript. Kornetov A.N. – critical revision of the manuscript for important intellectual content.

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Received 31.12.2021;
approved after peer review 30.03.2022;
accepted 25.05.2022