PIP5K2A (rs10828317) polymorphism in patients with alcohol dependence and affective disorders

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Alcohol dependence (AD) and affective disorders (ADs) are serious medical and socio-economic problems of modern society. It is hypothesized that both disorders share a common neurobiological basis. Phosphatidylinositol-4-phosphate-5-kinase type 2 alpha (PIP5K2A) plays an essential role in neuronal phosphoinositide signaling pathways. Nonsynonymous rs10828317 mutation of the PIP5K2A gene leads to conformational changes of the PIP5K2A protein and a decrease in the functional activity of this enzyme. In this study, we assessed the possibility of using the rs10828317 polymorphic variant of the PIP5K2A gene as a marker of AD and ADs.

Objective: *to study the associations of the PIP5K2A (rs10828317) polymorphism with AD and ADs clinical course.*

Patients and methods. *We enrolled 255 patients with AD and 325 patients with ADs. 126 patients with AD and 71 patients with ADs underwent a comprehensive clinical, clinical-dynamic, psychodiagnostic assessment using a set of clinical scales and tests, including Structured Interview Guide For The Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD), Alcohol Use Disorders Identification Test (AUDIT), The Obsessive-Compulsive Drinking Scale for craving in alcohol (OCDS).*

Results and discussion. *PIP5K2A (rs10828317) polymorphism in patients with AD was associated with the OCDS mean score after the inpatient treatment; in patients with ADs - with the severity of atypical depression symptoms assessed by SIGH-SAD at the time of admission.*

Conclusion. *The results of our pilot study indicate the involvement of PIP5K2A (rs10828317) polymorphism in the AD and ADs pathophysiology.*

Keywords: *affective disorders; alcohol dependence; polymorfism; PIP5K2A.*

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Alcohol dependence (AD) and affective disorders (ADs) are serious medical and socio-economic problems of the modern society [1].

According to the literature, there is a certain association between AD and ADs [2, 3]. Both disorders are hypothesized to share a common neurobiological basis. [4]. Analysis of the genome-wide association studies (GWAS) data demonstrates a considerable contribution of common gene variants to the risk of developing both substance dependence and mental disorders [5].

PIP5K2A (Phosphatidylinositol-4-phosphate-5-kinase type 2 alpha) plays an essential role in neuronal phosphoinositide signaling pathways. [6, 7, 8]. It regulates the functional activity of potassium KCNQ-channels, which are involved in maintaining the membrane potential of dopamine neurons [9, 10], and glutamate transporters EAAT3 [11], as well as the function of ionotropic glutamate receptors GluA1, the most important excitatory receptors in the central nervous system [12].

The *PIP5K2A* gene is localized in the 10p12 chromosomal region. Even though the works of several researchers demonstrate data on the absence of a contribution of *PIP5K2A* to the development of mental and behavioral disorders [13], there are also data on its association with schizophrenia [14, 15], bipolar disorder [16] and depressive disorder [17], as well as the effectiveness of the therapy of these diseases [18, 19].

The rs10828317 polymorphic variant of the *PIP5K2A* gene is a functional polymorphism in which amino acid substitution N251S leads to the protein conformation and, consequently, to a decrease in the functional activity of the PIP5K2A enzyme. This mutation was shown to play a role in the disturbances of the glutamatergic [11, 12] and dopaminergic [9] systems. Some studies have shown the association of the rs10828317 polymorphic variant of the *PIP5K2A* gene with schizophrenia [20] and depressive disorders [19].

We suggested that the dysfunction of PIP5K2A caused by the functional polymorphism rs10828317 may be associated with the pathogenetic mechanisms of developing AD and ADs as well as with the clinical characteristics of their progression.

Objective: to study the associations of the *PIP5K2A* (rs10828317) polymorphism with AD and ADs clinical course.

Patients and methods. Participants were recruited from the department of affective states and department of addictive states at the clinics of the Mental Health Research Institute, Tomsk National Research Medical Center (Tomsk, Russia). The study was carried out according to the protocol that was

approved by the local ethics committee of the Mental Health Research Institute (Protocol number №407 from 02.10.2018). Written informed consent was signed by all participants prior to the study.

We examined 255 patients with the diagnosis F10.2. – «Alcohol dependence» (AD), 325 patients with a depressive episode within the cluster F31, F32, F33 or dysthymia (F34.1) (ADs), and 356 mentally and somatically healthy individuals as a control group. The group of patients with AD included 229 men and 26 women (mean age – 41 [33; 51] years); the group of patients with ADs consisted of 261 women and 64 men (mean age – 52 [41; 58] years); the control group included 238 women and 118 men (mean age – 25 [21; 40] years).

Of all study participants, 126 patients with AD and 71 patients with ADs additionally underwent a comprehensive clinical, clinical-pathopsychological, clinical-dynamic assessment using a set of clinical scales and tests at two «examination points» during the period of treatment in the clinics: during the first week of therapy (after the relief of withdrawal symptoms in the case of seeking help in a state of alcohol withdrawal) and after 4 weeks of psychopharmacotherapy.

The SIGH-SAD (Structured Interview Guide For The Hamilton Depression Rating Scale, Seasonal Affective Disorders Version) scale was used for an objective quantitative assessment of the severity of depression and the dynamics of the state during therapy, taking into account typical and atypical depressive symptoms. The AUDIT (Alcohol Use Disorders Identification Test) test was used to identify alcohol-related disorders. The Obsessive-Compulsive Drinking Scale (OCDS) was used to measure patients' craving for alcohol over the previous week.

DNA was isolated using the standard phenol-chloroform method. Genotyping of the *PIP5K2A* rs10828317 was performed by real-time PCR on Applied Biosystems ™ QuantStudio ™ 5 Real-Time PCR System (Applied Biosystems, USA) based on the Core Facility «Medical genomics», using TaqMan1 Validated SNP Genotyping Assay kit (Applied Biosystems, USA).

Data processing was carried out using the Statistica12.0 for Windows (StatSoft Inc.,USA). To compare the studied groups, the Kruskal–Wallis tests and Pearson's chi-squared test with the Yates correction for continuity with the number of degrees of freedom equal to 1 as well as the Bonferroni correction when pairwise comparison of more than two groups were used. The distribution of genotypes for the studied polymorphic loci was checked for compliance with the Hardy–Weinberg equilibrium (HWE) using the chi-square test. The observed frequencies of genotypes in the studied groups correspond to those expected. For all analyzes, differences were considered statistically significant at $p<0.05$.

Results. We carried out an analysis of the distribution of the genotypes and alleles frequencies of the polymorphic variant *PIP5K2A* rs10828317 in patients with AD, ADs and in the control group (Table 1). When comparing the studied groups, significant differences were revealed in the distribution of genotypes ($\chi^2=10.11$, $p=0.039$), but not alleles ($\chi^2=5.67$, $p=0.059$) of the rs10828317 polymorphism of the *PIP5K2A* gene.

Pairwise comparison of the studied groups revealed significant differences between the groups of patients with AD and patients with ADs both in the distribution of genotypes ($\chi^2=7.07$, $p=0.029$) and alleles ($\chi^2=3.96$, $p=0.047$). The TT-genotype, like the T-allele, were more common in the group of patients with AD (52.55% and 71.76%, respectively) compared with the group of patients with ADs (41.85% and 66.31%, respectively). Allele T was also more common ($\chi^2=4.99$, $p=0.026$) in the group of patients with AD (71.76%) compared with the control group (65.73%). However, after the adjustment for multiple comparisons the statistical significance disappears.

Of all study participants, 126 patients with AD and 71 patients with ADs underwent a complex clinical, clinical-pathopsychological, clinical-dynamic assessment. Based on the results of this assessment, an analysis of the associations of *PIP5K2A* rs10828317 polymorphism with clinical characteristics of the patients was carried out.

We revealed an association of *PIP5K2A* rs10828317 with the scores of pathological craving for alcohol, assessed by the OCDS after the course of psychopharmacotherapy ($p=0.0001$) in patients with AD. Carriers of the TT-genotype showed higher scores of craving for alcohol (4 [0; 11]) compared with carriers of the CT and CC-genotypes (0 [0; 3.5] and 0 [0; 2 respectively) (Table 2).

Table 1. *Allele frequency and genotype distribution of rs10828317 polymorfic variant of the PIP5K2A gene in patients with AD and Ads and in control group, n (%)*

Genotypes/ alleles	Patients with AD (n=255)	Patients with ADs (n=325)	Control group (n=356)	χ^2, p
CC	23 (9,02)	30 (9,23)	45 (12,56)	$\chi^2=10,11$; p=0,039*
CT	98 (38,43)	159 (48,92)	154 (43,26)	
TT	134 (52,55)	136 (41,85)	157 (44,10)	
C	144 (28,24)	219 (33,69)	244 (34,27)	$\chi^2=5,67$; p=0,059
T	366 (71,76)	431 (66,31)	468 (65,73)	
HWE	$\chi^2=0,68$; p=0,41	$\chi^2=2,93$; p=0,09	$\chi^2=0,56$; p=0,45	

Note. Table 1–3: * – $p<0.05$ statistically significant by the Pearson's chi-square.

Table 2. *Associations of PIP5K2A (rs10828317) polymorphism with OCDS scores at the follow-up and AUDIT scores in patients with AD, Me [25; 75 percentiles]*

Index	Genotypes			p
	CC (n=23)	CT (n=48)	TT (n=55)	
AUDIT	27 [18; 36]	26,5 [22,5; 33]	29 [21; 33]	0,99
OCDS upon admission	38 [31; 47]	34,5 [28,5; 39]	34 [28; 41]	0,37
OCDS after 4 weeks	0 [0; 2]	0 [0; 3,5]	4 [0; 11]	0,0001*

Table 3. *Associations of PIP5K2A (rs10828317) polymorphism with SIGH-SAD severity of current depressive episode in patients with ADs, Me [25; 75 percentiles]*

SIGH-SAD	Genotypes			p
	CC (n=16)	CT (n=34)	TT (n=21)	
Upon admission				
Typical depressive symptoms	23 [17.5; 25.5]	20.5 [16; 25]	23 [16; 25]	0,70
Atypical depressive symptoms	7.5 [5.5; 15.5]	5 [4; 7]	6 [3; 9]	0.039*
Total score	31 [23.5; 43.5]	26.5 [22; 32]	30 [20; 32]	0.11
After 4 weeks				
Typical depressive symptoms	5 [2.5; 7]	4 [2; 8]	6 [3.5; 9.5]	0.48
Atypical depressive symptoms	1.5 [0.5; 4.5]	2 [0; 3]	1 [0; 4]	0.87
Total score	7 [3; 10]	6 [3; 11]	6 [5; 12]	0.72

In patients with ADs, we revealed an association of *PIP5K2A* rs10828317 with the severity of atypical depressive symptoms at the time of admission to hospital (p=0.039) (Table 3). Carriers of the CC-genotype of rs10828317 had higher scores when assessed for atypical depressive symptoms (7.5 [5.5; 15.5]) in comparison with carriers of the CT and TT-genotypes (5 [4; 7] and 6 [3; 9], respectively).

Discussion. The *PIP5K2A* gene is a candidate gene for a few mental disorders. Its effect has been most proven in schizophrenia [14, 15] and bipolar affective disorders [16] and, to a lesser extent, in depressive disorders [19, 20].

The polymorphic variant rs10828317 of the *PIP5K2A* gene is a missense mutation. It leads to amino acid substitution and, consequently, to a decrease in the functional activity of the PIP5K2A enzyme. It has been proven that this mutation leads to disturbances in the functioning of glutamate transporters [11], glutamate receptors [12] and KCNQ channels [9].

In addition, imbalance of a number of components of the PI3K/AKT1 signaling pathway (PIK3C3, PIP5K2A, PLCG1, SYNJ1, IMPA2, AKT1, GSK3B, TCF4), which are activated both by neurotrophic factors and through glutamate receptors, is detected in depressive disorders and alcohol use disorders [5].

In the present study we have shown for the first time the difference in the carriage of the rs10828317 polymorphism of the *PIP5K2A* gene between the groups of patients with AD, ADs and healthy controls. For the first time, an assessment of associations of this polymorphism with clinical characteristics of the course of the studied disorders was carried out.

When comparing the studied groups, statistically significant differences in the distribution of genotypes of the polymorphic variant rs10828317 of the *PIP5K2A* gene were revealed. In addition, we demonstrated an association of the polymorphic variant rs10828317 of the *PIP5K2A* gene with the scores of craving for alcohol on the OCDS scale after a course of psychopharmacotherapy in patients with AD, and an association of this polymorphism with the severity of atypical depressive symptoms at the time of admission to hospital assessed with the SIGH-SAD scale in patients with ADs.

Limitations of the study. Even though screening for the carriage of the studied polymorphism was carried out in rather large groups of patients, the results concerning associations with clinical characteristics and response to therapy are preliminary and require further study in larger patient samples.

Conclusion. The obtained pilot results indicate the involvement of the rs10828317 polymorphic variant of the *PIP5K2A* gene in the pathophysiological processes of the development of alcohol use disorders and affective disorders.

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Conflict of Interest Statement

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