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Article

Genetic Associations of the Polymorphic Variant of the *DRD2* (rs1800497) Gene with Forms of Suicidal Behavior in Patients with Alcohol Dependence

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Abstract: Suicide is a serious public health problem. A deeper understanding of the underlying mechanisms and processes that lead to suicidal behavior is crucial for the development of effective preventive strategies. The study and identification of biomarkers will help in understanding the underlying processes or changes associated with suicide, however, studies linking biomarkers to suicide are limited and fragmented. **Objective**- To study the genetic associations of the polymorphic variant of the DRD2 gene (rs1800497) with forms of suicidal behavior in patients with alcohol dependence**.** Materials and methods**:** The association of polymorphic variants of the gene *DRD2* (rs1800497) was analysed in patients with alcohol dependence syndrome, with a history of suicidal behavior and without it, living in the Republic of Bashkortostan, who were treated at the Republican Narcological Dispensary in the period from 2019 to 2021. Results: the presence of suicidal tendencies was detected in 39% of patients (136/344). 30% (42/136) were classified as patients with external and internal forms of suicidal behavior, 70% (94/136) had only internal forms of suicidal behavior. Carriages of the CC and TT genotypes of the *DRD2* gene (rs1800497) are characterized by a lower frequency of occurrence of all forms of suicidal behavior than carriages of CT genotype. Also, carriages of the CC genotype of the *DRD2* gene (rs1800497) are characterized by a lower frequency of occurrence of external forms of suicidal behavior than carriages of CT and TT genotypes. Conclusions. The data we present indicate the possible contribution of genetic factors to the risk of suicidal behavior in individuals with alcohol dependence syndrome. There is a need for further research to explain the relationships between the circadian rhythm system, alcohol use disorders and suicidal behavior.

Keywords: *alcoholism; alcohol withdrawal; suicide; DRD2; suicidal behavior.*

1. Introduction

The annual global mortality rate from suicide is 14.5 suicides per 100,000 people, which is approximately one death worldwide every 40 seconds [1]. According to statistical data, the suicide rate in the Russian Federation at the end of the last century significantly exceeded the critical level (41.5 cases in 1995, 48.9 deaths in 2008) and tended to remain high until the end of the first decade of the 21st century [2]. The suicide rate in Russia in 2018 was 12.2 per 100 thousand people [2], and in 2019 it corresponds to a rate of 11.6 per 100 thousand people; however, these data do not exclude the importance of further study of this problem [3, 4].

Suicidal behavior is often formed in the structure of mental disorders and disorders caused by alcohol consumption [5]. Among people dependent on psychoactive substances, the risk of developing suicidal thoughts and attempts is especially high [6]. So, H.M. Inskip et al. showed that the lifetime risk of suicide in people with alcohol dependence was higher than in people with mood disorders [7]. More than 40% of all patients with alcohol dependence have reported a suicide attempt [8].

Several studies prove the connection of the genetic component and changes in the functioning of the neurotransmitter systems of the brain with suicidal behavior. Early molecular genetic studies of suicidal behavior focused on genes of the serotonergic system, because of biochemical evidence of involvement of serotonergic neurotransmission in this kind of behavior. There are also studies of cerebrospinal fluid in patients that have confirmed the possible involvement of the dopaminergic system in suicidal behavior. The DRD2 gene, located on chromosome 11 11q23.2, has a length of 65577 bp was studied in a group of patients with alcohol dependence syndrome and persons without alcohol dependence. The E8 A=A genotype was found to be associated with an increase in suicide attempts and with increased rates of anxiety and depression in a group of alcohol-dependent individuals [9].

Currently, there is an insufficient number of studies proving the genetic role of various forms of suicidal behavior in patients with alcohol dependence syndrome, so it is advisable to consider this problem, given its relevance and prevalence in the world.

2. Objective

To study the genetic associations of the polymorphic variant of the *DRD2* gene (rs1800497) with forms of suicidal behavior in patients with alcohol dependence.

3. Materials and Methods

The study included 344 patients living in the Republic of Bashkortostan, hospitalized at the Republican Clinical Narcological Dispensary in the period from 2019 up to 2021. The average age of the patients was 42.48 ± 7.8 years; 23% (77/344) were women, 77% (267/344) were men.

The study was approved by the local ethics committee of the Bashkir State Medical University. Protocol No. 2 dated February 27, 2019.

Inclusion criteria: presence of a verified diagnosis F10.2 "Alcohol dependence syndrome"; the period of clinical observation in the drug treatment service is more than a year; age not younger than 18 and not older than 55 years; no less than 7 and no more than 14 days from the date of hospitalization; no use of psychotropic medications within 3 days before the examination.

Non-inclusion criteria: refusal to participate in the study; presence of alcohol withdrawal syndrome at the time of examination; the patient meets the diagnostic criteria for dependence on a psychoactive substance other than alcohol, nicotine and caffeine; the presence of reasons that make verbal contact difficult; the presence of comorbid mental pathology: schizophrenia, schizotypal states, delusional disorders (F20-F29), dementia (F00-F03), mental retardation (F70-F79), with severe somatic pathology of the cardiovascular, respiratory, endocrine systems, gastrointestinal tract and urinary system.

Exclusion criteria: refusal to participate in the study after it began; identification of newly discovered circumstances during a clinical trial.

Molecular genetic studies were conducted at the National Medical Research Centre for Psychiatry and Neurology named after. V.M. Bekhterev (St. Petersburg).

Genetic testing: determination of polymorphic gene variants was conducted using the real-time polymerase chain reaction method. The biological material for determining polymorphic gene variants was whole blood taken in a vacuum tube with EDTA K3. DNA was isolated from whole blood lymphocytes, pre-washed reagents for pre-treatment of whole peripheral and umbilical cord blood "Hemolytic" (FBUN Central Research Institute of Epidemiology of Rospotrebnadzor). Further extraction of nucleic acids was carried out with a set of reagents for DNA/RNA isolation "Ribo-PREP" (FBUN Central Research Institute of Epidemiology of Rospotrebnadzor). Analysis of the results was conducted using RotorGene Q6 plex software using parameters specified by the manufacturer. Processing of molecular genetic study data was carried out using IBM SPSS 20.0.

Next, the groups of patients were divided according to the criterion of the presence/absence of suicidal behavior and, in accordance with the results of clinical interviews, graded depending on the form of suicidal behavior according to the classification of P. B. Zotov and S. M. Umansky (2011). Zotov P.B. and Umansky S.M (2011) distinguish external and internal forms of suicidal behavior [5]. Internal forms include: antivital experiences; suicidal thoughts; suicidal thoughts; suicidal intentions. External forms: suicide attempts; completed suicide.

4. Results

We have detected suicidal tendencies in 39% of patients (136/344). 30% (42/136) were classified as patients with external and internal forms of suicidal behavior, 70% (94/136) had only internal forms of suicidal behavior. Structure of suicidal behavior are presented in figure 1.

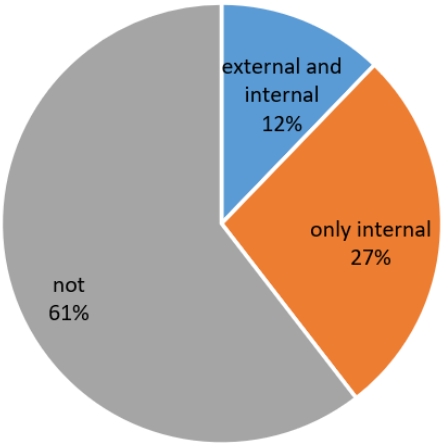

Figure 1. Structure of suicidal behavior

Carriages of the CC and TT genotypes of the *DRD2* gene (rs1800497) are characterized by a lower frequency of occurrence of all forms of suicidal behavior than carriages of CT genotype. The results are presented in the table 1.

Table 1. Incidence of suicidal behavior in owners of different genotypes of the DRD2 gene (rs1800497)

The symptom	Genotypes; n (%)			Pearson's chi-squared test	p-value
	CC	CT	TT		
All forms of suicidal behavior	72 (34)	46 (54)	18 (35)	10.051	0.007
Not	136	39	33		
All	208	85	51	-	-

Also, carriages of the CC genotype of the *DRD2* gene (rs1800497) are characterized by a lower frequency of occurrence of external forms of suicidal behavior than carriages of CT and TT genotypes. The results are presented in the table 2.

Table 2. Incidence of external and internal forms of suicidal behavior in owners of different genotypes of the DRD2 gene (rs1800497)

The symptom	Genotypes; n (%)			Pearson's chi-squared test	p-value
	CC	CT	TT		
External and internal forms of suicidal behavior	16 (7)	18 (21)	8 (15)	10.911	0.004
Not	192	67	43		
All	208	85	51	-	-

5. Discussion

The role of dopamine receptor genes in suicidal behavior has also been described by other authors [10]. There is evidence of the importance of dopamine in the formation of alcohol dependence. Andrzej Rosiewicz et al. in a study of a sample of 169 alcohol addicts in Poland, polymorphisms in the *DRD2* and *ANKK1* genes were analyzed and determined that persons with alcohol dependence, in whose history there was at least one suicidal attempt, were characterized by a significantly higher frequency of the TG-A2 haplotype compared to persons whose alcohol dependence was not associated with suicidal behavior [11]. Other authors point to the association of the *DRD2* gene and the severity of alcohol withdrawal syndrome, which in turn is associated with the risk of suicidal behavior [12]. The connection of the *DRD2* gene and suicide in the German population was shown in a study by Monica Johann et al [13]. All this suggests the need for further investigation of the role of the dopamine system in suicidal behavior in patients with alcohol dependence.

Conclusions

The data we present indicate the possible contribution of genetic factors to the risk of suicidal behavior in individuals with alcohol dependence syndrome. There is a need for

further research to explain the relationships between the circadian rhythm system, alcohol use disorders and suicidal behavior.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.
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