SLC6A3 (DAT1) as a novel candidate biomarker gene for suicidal behavior: a pilot study

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Abstract

Objective This study aims to estimate the contribution of 11 polymorphisms in the genes SLC6A4 (5HTT), HTR1A, HTR2A, HTR1B, SLC6A3 (DAT1), DRD4, DRD2, COMT and BDNF to suicidal behavior and severity of symptoms of depression and anxiety in Russian population.

Methods The study was performed on 100 patients with repeated suicide attempts and 154 controls. The SNP and VNTR genotyping was carried out using locus-specific PCR. Logistic regression approach was applied to establish associations between gene polymorphisms and risk of suicidal attempts. Negative binomial regression was used to analyze association between genotypes and count variables: severity of depressive symptoms, personal anxiety and situational anxiety.

Results We have first found an association between SLC6A3 (DAT1) 40 bp VNTR locus and suicidal behavior. This association was significant in the co-dominant (P = 0.006), dominant (P = 0.001), over-dominant (P = 0.004) and log-additive (P = 0.004) models, LL genotype played a protective role (OR = 0.48, 0.29–0.82). Difference in the genotypes distribution of COMT rs4680 was significant in the co-dominant (P = 0.04), dominant (P = 0.013) and log-additive (P = 0.02) models, and AA genotype might protect against suicide (OR = 0.49, 0.26–0.91). SLC6A4 5-HTTLPR+rs25531 locus was significant only in the recessive model (P = 0.024) and also affected the severity of symptoms of depression (P = 0.044) and personal anxiety (P = 0.029).

Conclusions Our results suggest that allelic variants of SLC6A3, COMT and SLC6A4 genes might be considered as risk factors for suicidal attempts.

1. Introduction

According to the World Health Organization, more than 800 000 people die from suicide each year [1]. Many family, twin, and adoption studies provide evidence for familial transmission of suicide and suicidal behavior [2-6]. The contribution of genetic risk factors was confirmed even after controlling for hereditary mental disorders [7]. The aggregation of suicide in families also cannot be fully explained by a similar environment [8]. Molecular studies have shown that suicide attempts could be associated with altered serotonin and dopamine transmission [9-12]. Given the above data, the search for an association between suicidal behavior and genes encoding important pathways of serotoninergic and dopaminergic transmission is relevant.

The promoter region of the serotonin transporter gene (SLC6A4/5-HTT) contains the variable number tandem repeats (VNTR) polymorphism. Short (S) allele with 14 repeats is associated with lower expression activity compared to long (L) allele with 16 repeats [13, 14]. Later single nucleotide polymorphism (SNP) A → G (rs25531) was detected within the 6th repeat of the S- and L-alleles. As was shown, the expression level of the LG allele is lower compared to LA allele [15]. A recent meta-analysis

demonstrated a lack of association between low-expressing alleles or genotypes and suicidal behavior, but low-expressing alleles (S + LG) were associated with Violent Suicide Attempt [16].

Polymorphism C1019G (rs6295) exists in the promoter region of the HTR1A gene. It might enhance or decrease gene expression depending on the location on the presynaptic or postsynaptic membrane [17, 18]. Post-mortem study has discovered that the HTR1B gene polymorphism G861C (rs6296) affects gene expression activity and as a result changes the density of the receptors [19]. In the case of HTR1A gene polymorphism A1438G (rs6311), it was shown that the A-allele increases the promoter activity [20]. Association studies for these genes were also performed. Meta-analyses of these investigations detected a significant association between HTR2A rs6311 and suicidal behavior [21] but failed to find any associations for HTR1A rs6295 and HTR1B rs6296 polymorphisms [22, 23]. Another meta-analysis did not confirm the previously suggested association between HTR2A rs6311 and attempted suicide in the general population [24].

A 40 bp VNTR-polymorphism exists in the 3'-UTR region of the dopamine transporter gene (SLC6A3/DAT1). Several studies have confirmed the effect of the length of this locus on gene expression, although contradictory results have been obtained [25-28]. It was shown that the 9R-allele may result in a high risk of depression and angry-impulsive personality traits [29, 30]. The dopamine receptor gene (DRD4) contains a 48 bp VNTR-polymorphism in exon 3 and 120 bp VNTR polymorphism in the promoter region. The 7-repeat variant of the DRD4 48 bp VNTR-polymorphism was found to be associated with such personality traits as impulsivity, aggression, depression and novelty-seeking behavior, but not with suicidal behavior [31-33]. DRD4 120 bp VNTR polymorphism might affect gene expression activity—the long allele is associated with a lower expression level than the short allele [34]. The density of the DRD2 receptors in the striatum depends on the allelic variant of the rs1800497 (C/T) polymorphism. It was shown that T-allele carriers have a lower density of DRD2 receptors [35]. The DRD2 rs1800497 polymorphism is associated with impulsivity and suggested to be related to suicidal attempts [36, 37]. The enzyme catechol-O-methyltransferase (COMT) plays an important role in dopamine metabolism. SNP rs4680 (G/A or Val/Met) in the COMT gene leads to reduced enzyme activity [38]. A meta-analysis of six studies has demonstrated that the COMT rs4680 polymorphism has a modestly significant association with suicidal behavior [23]. A recent meta-analysis demonstrated a lack of association between COMT rs4680 polymorphism and suicidal behavior in the overall population, but this locus was shown to be a risk factor in Asian populations [39].

The BDNF gene encoding the brain-derived neurotrophic factor contains a common polymorphism rs6264 which leads to the replacement of methionine with valine (Val66Met). Met-allele is associated with decreased protein activity [40] and possibly with suicide attempts [41].

Research findings on genetic risk factors for suicidal behavior are inconsistent and some results depend on the ethnicity of the participants. This study aims to estimate the contribution of 11 polymorphisms in the genes SLC6A4 (5HTT), HTR1A, HTR2A, HTR1B, SLC6A3 (DAT1), DRD4, DRD2, COMT and BDNF to

suicidal behavior and severity of symptoms of depression and anxiety in Russian population. As described above, all polymorphisms under study affect gene expression, protein product activity or were shown to be associated with personality traits.

2. Methods

2.1 Subjects

A sample of patients (N = 100) of East Slavic origin who had attempted suicide at least two times and were monitored by a psychotherapist was used for this study. All blood samples were collected with the informed consent of the investigated persons after a participant's personal statement signature. The Ethics Committee of the Institute of Molecular Genetics (Institute of Molecular Genetics, Russian Academy of Sciences, Kurchatov sq. 2, Moscow, Russia) approved the study (protocol 03\19, 19 February 2019).

A survey of patients and blood samples was carried out at the Moscow Research and Clinical Center for Neuropsychiatry of the Healthcare Department of Moscow. Depressive symptoms were evaluated with help of Hamilton's Depression Rating Scale (HAMD) and Beck's Depression Inventory (BDI). Spielberger's test was used for evaluation of the degree of situational and personal anxiety. The patients were diagnosed with the following: depressive episode (F 32.1), N=22; recurrent depressive disorder (F 33.1), N=22; mixed anxiety and depressive disorder (F 41.2), N=13; bipolar disorder (F 31.3), N=10; schizopathic disorder (F 21.8), N=6; emotionally unstable personality disorder (F 60.31), N=5; other, N=24. Demographic and clinical characteristics of patients are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients with suicidal behavior

n	total	100
	female	80
	male	20
Age, years	min	18
	max	77
	mean, SD	31.54±11.13
BDI	min	8
	max	53
	mean, SD	28.85±9.58
HAMD	min	7
	max	35
	mean, SD	21.19±5.22
Situational anxiety	min	25
	max	80
	mean, SD	55.52±12.93
Personal anxiety	min	25
	max	80
	mean, SD	56.44±10.05

BDI — Beck's Depression Inventory

HAMD — Hamilton’s Depression Rating Scale

The control group (N = 154) was a sample of the East Slavic population of the city of Moscow and the regions of Central Russia (59 men (38.3%) and 95 women (61.7%); mean age: 62.19 ± 9.45 years). The control group included people over the age of 40 to reduce the likelihood of the presence of a genetic predisposition to suicide, which has not yet manifested. Details of patients and controls characteristics and genotyping results are shown in Supplementary File 1.

2.2 DNA isolation and genotyping

Genomic DNA was obtained from 250 μL of EDTA-anticoagulated venous blood using innuPREP Blood DNA Mini Kit (Analytik Jena AG, Germany), according to the manufacturer's recommendations.

The SNP and VNTR genotyping was carried out using locus-specific PCR as described previously [42-47].

2.3 Statistical analysis

Hardy–Weinberg equilibrium calculator software (https://wpcalc.com/en/equilibrium-hardy-weinberg/) was used to calculate the correspondence of the genotype distribution in the population sample to the Hardy–Weinberg equilibrium (HWE). Logistic regression approach was applied to establish associations between gene polymorphisms and risk of suicidal attempts. Negative binomial regression was used to analyze association between genotypes and count variables: severity of depressive symptoms (HAMD and BDI scales), personal anxiety and situational anxiety. The statistical significance of polymorphisms was established with a likelihood-ratio test. Akaike information criterion (AIC) was used to identify the model that best fits the data. All calculations were performed in the R statistical environment.

The following genetics models were tested:

1. Co-dominant. This model assumes that each genotype can influence risk independently of the others.
2. Common allele homozygotes were tested against rare allele homo- and heterozygotes.
3. Rare allele homozygotes were tested against common allele homo- and heterozygotes.
4. Over-dominant. Heterozygotes were tested against both homozygotes.
5. Log-additive. A trend test for the genotypes, according to this model, each allele changes the risk in an additive manner (i.e. the presence of two alleles double the risk compared to the presence of only one allele). The test was based on a logistic regression model and genotypes were coded as 0, 1, or 2 depending on the amount of minor alleles.

The strength of associations between allelic variants of studied polymorphic loci and suicidal behavior was estimated using odds ratios (ORs), with the corresponding 95% confidence intervals (95% CIs). All tests were conducted at a level of significance $p < 0.05$.

Given the data suggesting the effect of length of SLC6A3 40 bp VNTR locus on gene expression and high activity of the 10R allele compared with the 9R allele, we classified cases and controls as carriers of the long (≥10) and short (<10) alleles.

Because of the complexity of SLC6A4 organization, we analyzed the distribution frequencies of its allelic variants according to their functional characteristics. To verify whether alleles with low or high expression activity are associated with suicidal behavior, we grouped alleles and genotypes according to their expression levels: high (L_A) and low (S and L_G) alleles with high and low expression activity, respectively, and high/high (L_A/L_A), high/low (L_A/S_A, L_A/L_G) and low/low (S_A/S_A, S_A/L_G, L_G/L_G) genotypes. The alleles of the DRD4 48 bp VNTR were grouped into long (≥7) and short (<7) allelic variants.

3. Results

All polymorphisms were in the Hardy–Weinberg equilibrium in control and case samples. Table 2 represents the most statistically significant results of the logistic regression analysis.

We have first found an association between VNTR-polymorphism of the SLC6A3 (DAT1) gene and suicidal behavior. The short allele (S) was more common in cases than it was in the control group (26% vs 16.6%). LL genotype was associated with lower risk of suicide (OR = 0.48, 0.29–0.82). The difference in genotype distribution of this locus was significant in the co-dominant (P = 0.006), dominant (P = 0.001), over-dominant (P = 0.004) and log-additive (P = 0.004) models.

Table 2. Association between genes of dopamine and serotonin systems and suicidal attempts

Genotype	Control, n (%)	Suicide, n (%)	LRT, P	ORs, P, 95% CI
SLC6A3 (DAT1) 40 bp VNTR				
LL	113 (69.3)	52 (52)	co-dominant: 10.16, 0.006**	0.48, 0.005, 0.29–0.82
LS	46 (28.2)	44 (44)	dominant: 10.54, 0.001**	1.998, 0.009, 1.19–3.37
SS	4 (2.5)	4 (4)	over-dominant: 8.14, 0.004**	1.66, 0.483, 0.4–6.78
			log-additive: 8.05, 0.004**	
COMT rs4680				
AA (Met/Met)	48 (29.4)	17 (17)	co-dominant: 6.42, 0.04*	0.49, 0.025, 0.26–0.91
GA (Val/Met)	78 (47.9)	53 (53)	dominant: 6.11, 0.013*	1.23, 0.418, 0.75–2.02
GG (Val/Val)	37 (22.7)	30 (30)	log-additive: 5.39, 0.02*	1.46, 0.188, 0.83–2.56
SLC6A4 5-HTTLPR + rs25531				
high/high	49 (31.2)	35 (35)	recessive: 5.06, 0.024*	1.19, 0.528, 0.7–2.02
high/low	67 (42.7)	50 (50)		1.34, 0.251, 0.81–2.22
low/low	41 (26.1)	15 (15)		0.5, 0.038, 0.26–0.96
BDNF rs6264				
CC (Val/Val)	183 (70.7)	61 (61)	recessive: 2.82, 0.093+	0.65, 0.08, 0.4–1.05
CT (Val/Met)	69 (26.6)	32 (32)	log-additive: 2.86, 0.09+	1.3, 0.312, 0.78–2.14
TT (Met/Met)	7 (2.7)	7 (7)		2.71, 0.069, 0.93–7.93

LRT— likelihood-ratio test, ORs—odds ratios, CIs—confidence intervals

** P < 0.005, * P < 0.05, + P < 0.1

Another gene of the dopaminergic system associated with suicide attempts was the COMT gene. The G-allele (Val) frequency of COMT rs4680 was higher in the group of cases compared with the control group (56.5% vs 46.6%). AA (Met/Met) genotype protected against suicidal behavior (OR = 0.49, 0.26–0.91). The effect of COMT rs4680 on the risk of suicidal attempts was significant in the co-dominant (P = 0.04), dominant (P = 0.013), and log-additive (P = 0.02) models.

The high expressed allele of SLC6A4 (5HTT) gene was slightly more common in patients with suicidal behavior than it was in controls (60% vs 52.5%) and low/low genotype protected against suicide (OR = 0.05, 0.26–0.96). Genotype distribution of SLC6A4 5-HTTLPR+rs25531 polymorphism showed a significant difference only in the recessive model (p = 0.024).

We have found that the T-allele of BDNF rs6264 was more common in the cases compared to the control group (23% vs. 16%), CC genotype tends to be less common, while frequencies of CT and TT genotypes are higher in the group of cases. However, the difference in genotype distribution was not statistically significant.

No significant associations between suicidal behavior and DRD2 rs1800497, DRD4 120 bp VNTR and 48 bp VNTR, HTR1A rs6295, HTR2A rs6311 and HTR1B rs6296 alleles and genotypes were discovered. All results of genotyping of cases and controls are shown in Supplementary file 1.

To determine the effect of studied polymorphisms on the count variables, such as severity of depressive and anxiety symptoms, we conducted the negative binomial regression analysis. We observed a significant effect of SLC6A4 5-HTTLPR+rs25531 on depression symptoms (P = 0.044) and personal anxiety (P = 0.029). We have also found significant associations between DRD4 48 bp VNTR-polymorphism and situational anxiety (P = 0.039) (Figure 1). [insert Figure 1.] Although SLC6A3 (DAT1) and COMT genes were significant for the risk of suicidal attempts they showed a lack of association with the severity of the symptoms of depression, situational anxiety, and personal anxiety. The most significant results of this analysis are shown in Table 3.

Table 3. Association between genes of dopamine and serotonin systems and severity of depressive, situational anxiety and personal anxiety symptoms

Scale	Gene	Polymorphism	LRT	P
HAMD	SLC6A4 (5HTT)	5-HTTLPR + rs25531	6.29	0.044*
Personal anxiety	SLC6A4 (5HTT)	5-HTTLPR + rs25531	7.09	0.029*
	HTR1B	rs6296	5.03	0.081+
Situational anxiety	DRD4	48 bp VNTR	6.46	0.039*
	SLC6A4 (5HTT)	5-HTTLPR + rs25531	3.85	0.146
	HTR1A	rs6295	4.26	0.119

LRT— likelihood-ratio test, ** P < 0.005, * P < 0.05, + P < 0.1

4. Discussion

Genes related to neurotransmission and neurotrophic function have been widely studied in various mood and behavior disorders. To confirm possible associations studied previously and find out new

associations, we investigated SLC6A3 (40 bp VNTR), DRD2 (rs1800497), DRD4 (120 bp VNTR and 48 bp VNTR), COMT (rs4680), SLC6A4 (5-HTTLPR+rs25531), HTR1A (rs6295), HTR2A (rs6311), HTR1B (rs6296) and BDNF (rs6264) polymorphic loci in patients with suicidal behavior. The study was carried out with a sample of patients of East Slavic origin from Central Russia who had attempted suicide at least two times. We have supposed that the repeated suicidal attempts are not the result of impulsivity or mood disorders only but show the genetic predisposition to suicidal behavior. We have found statistically significant associations between suicidal behavior and SLC6A3 (40 bp VNTR), COMT (rs4680), and SLC6A4 (5-HTTLPR+rs25531) loci.

Although the association between SLC6A3 40 bp VNTR-polymorphism and mood disorders, as well as personality traits, was described [29, 30], there was no information about an effect of this locus on suicidal tendencies. We discovered a strong association between the presence of short (<10 repeats) allele and suicidal behavior. The short allele (S) was more common in cases and carriers of LL genotype had a lower risk of suicide (OR = 0.48, 0.29–0.82). Given the data of low expression activity of the 9R-allele [28], we can suppose that suicidal behavior may be associated with dopamine transporter deficiency and consequently with increased dopamine signalling.

Our results are opposite to the results of the meta-analysis that demonstrated an association between Met (A) allele of COMT rs4680 and suicidal attempts [23]. The authors draw attention to the dependence of the results on the inclusion of all six studies. When five of the six studies were individually excluded from the analysis relationship between COMT Met-allele and suicide was no longer significant. The latest meta-analysis showed lack of association between this locus and suicide [39]. However, the AA (Met/Met) genotype played a protective role (OR = 0.49, 0.26–0.91) in Russian cohort used in the present study.

According to results of recent meta-analysis SLC6A4 5-HTTLPR+rs25531 has no effect on suicidal behavior [16]. However, in the Russian cohort, this locus showed an association with suicide in the recessive model. Homozygous genotype with low expression activity (low/low) played a protective role in our samples (OR = 0.5, 0.26–0.96).

In our samples Met-allele of BDNF rs6264 was more common in the cases compared to the control group, which is consistent with a meta-analysis showed the risk of suicide in carriers of the Met-allele [41]. But the difference in genotypes distribution was not statistically significant in the present study.

The effect of dopamine receptor genes polymorphism on suicidal behavior is not well understood. Although some studies have shown an association between DRD2 rs1800497 or haplotypes with this SNP and suicidal behavior [36,37] no differences between allelic and genotype frequencies of this locus in our samples of patients and controls were found. Just like our research, previous studies failed to find an association between DRD4 48 bp VNTR-polymorphism and suicidal attempts [31, 33]. We also did not find DRD4 120 bp VNTR to be associated with suicide. In our knowledge, this is the first study aimed to establish if the DRD4 120 bp VNTR polymorphism is related to suicidal behavior.

Our data on the lack of association between HTR1A rs6295 and HTR1B rs6296 polymorphisms and suicide are consistent with previous meta-analyses [22, 23]. Contrary to the results of a meta-analysis showing a link between HTR2A rs6311 and suicidal behavior [21], we did not find statistically significant differences. These results are consistent with a more recent meta-analysis [24].

It was previously shown that all of these genes might be associated with major depression, although conflicting results have been obtained. We tried to verify if these loci affect severity of depressive and anxiety symptoms in patients with suicidal behavior. We observed an effect of SLC6A4 5-HTTLPR+rs25531 locus on depressive and personal anxiety symptoms and an effect of DRD4 48 bp VNTR-polymorphism on situational anxiety. SLC6A3 (DAT1) and COMT genes were associated with the risk of suicide but had no effect on the severity of symptoms of depression and anxiety. These results suggest that an effect of these loci on suicidal attempts is not explained by their effect on severity of the mood disorder.

This study has several limitations. The sample of patients consisted of 100 people, and the control group consisted of 154 people, which is not enough to test the interactions between genes. Further studies conducted using more large samples and considered more factors are required to verify if these polymorphic loci are risk factors only for suicidal behavior or they increase the risk of suicide via their effect on the severity of mental illness.

Declarations

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Supplementary information

Supplementary file 1.xlsx includes genotyping results, the age and gender of each study participant, as well as diagnoses and estimates of the severity of symptoms of depression and anxiety of patients with suicidal behavior.

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Figures

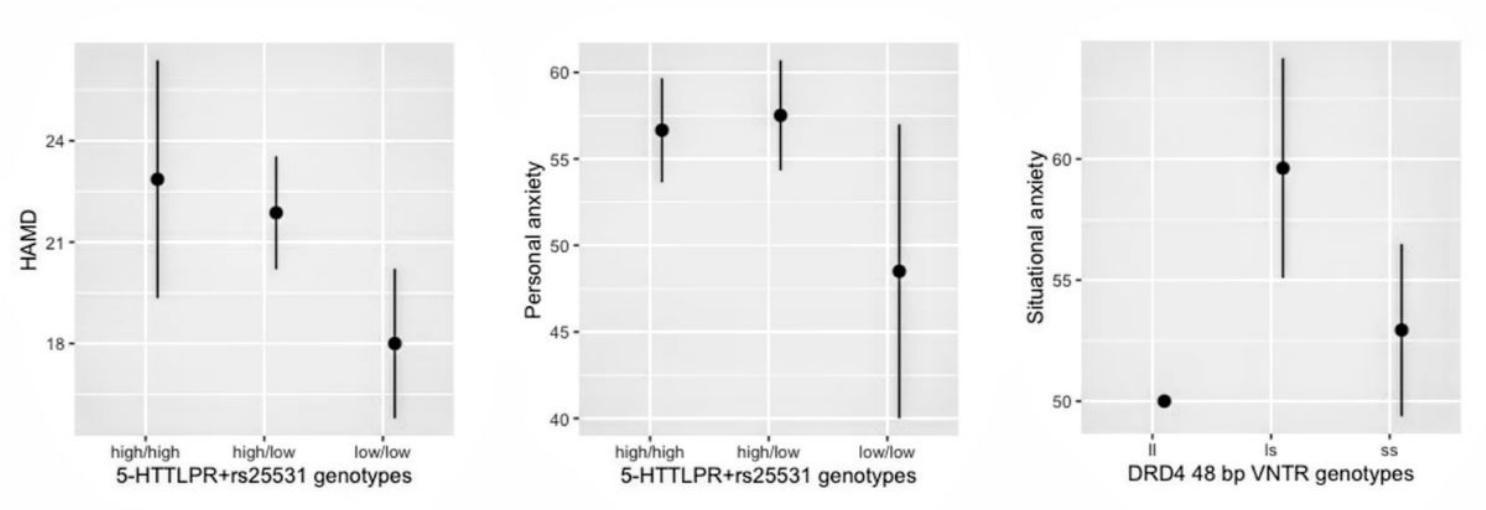

Figure 1

The distribution of the depression (HAMD scale) and anxiety symptoms with the SLC6A4 and DRD4 genotypes. The ordinate numbers designate the scores according to the Hamilton's Depression Rating Scale (HAMD) for depressive symptoms and subscales of Spielberger's test for anxiety symptoms.

Supplementary Files

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- Supplementaryfile1.xlsx