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EXPERIENCE OF USING THE MOLECULAR GENETIC STUDIES TO ASSESS THE RISK OF SUICIDE

Abstract. In the recent decades, there has been widespread the opinion that genetic markers of the suicidal behavior (suicide, suicidal attempts, suicidal thoughts) can be used to predict the suicidal behavior.

The purpose of the study was to determine the possibility of using the method of molecular genetic research to assess the risk of suicide in men of 18–27 years.

The study used the case-control method. The control group included 100 men of 18–27 years who never had mental disorders. The suicide group included the persons who committed highly traumatic methods of self-harm and were motivated to commit suicide (30 persons). DNA isolation was performed using a NucleoSpin Blood kit (Macherey–Nagel, Germany) according to the manufacturer's protocol. Each DNA sample was analyzed for polymorphism by allelic discrimination using the real-time polymerase chain reaction (PCR).

The frequencies of occurrence of genotypes and alleles of the following genes were analyzed*: HTR1A*, rs6295 (G/C); *BDNF*, rs6265 (G/A); *COMT*, rs4680 (G/A); *SKA2*, rs7208505 (C/T); *SLC6A4* (*5HTT*), rs25531 (T/C); *5HTR2A*, rs6313 (G/A); *TPH2*, rs4570625 (G/T); *TPH1*, rs1800532 (G/T).

A statistically significant difference was found for the frequency of occurrence of genotypes and alleles of the rs25531 polymorphism of the *SLC6A4* (*5HTT*) gene. The chance of being in the suicide group with a heterozygous genotype (T/C) carriage was 2.346 times higher.

The significance of the rs25531 polymorphism of the *SLC6A4* (*5HTT*) gene for the formation of the suicidal behavior was confirmed.

Keywords: molecular genetic research, suicide, genotype, polymorphism, alleles

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ВОПЫТ ВЫКАРЫСТАННЯ МАЛЕКУЛЯРНА-ГЕНЕТЫЧНЫХ ДАСЛЕДАВАННЯЎ ДЛЯ АЦЭНКІ РЫЗЫКІ САМАГУБСТВА

Анатацыя. У апошнія дзесяцігоддзі шырока распаўсюдзілася меркаванне, што генетычныя маркеры суіцыдальных паводзін (суіцыд, суіцыдальныя спробы, суіцыдальныя думкі) можна выкарыстоўваць для ацэнкі рызыкі самагубства.

Мэта даследавання – ацаніць магчымасць выкарыстання метаду малекулярна-генетычнага даследавання для ацэнкі рызыкі самагубства.

У даследаванні выкарыстоўваўся метад кантролю за выпадкамі. У кантрольную групу ўваходзілі 100 чалавек 18–27 гадоў, якія ніколі не мелі псіхічных разладаў, у групу самагубцаў – 30 чалавек, якія здзейснілі траўматычныя метады самапашкоджання з выражаным намерам здейсніць самагубства. Вылучэнне ДНК праводзілася з выкарыстаннем набору NucleoSpin Blood (Macherey-Nagel, Нямеччына) у адпаведнасці з пратаколам вытворцы. Кожны ўзор ДНК аналізавалі на паліморфізм шляхам алельнай дыскрымінацыі з выкарыстаннем ланцуговай рэакцыі палімеразы ў рэжыме рэальнага часу. Былі прааналізаваны частоты ўзнікнення генатыпаў і алеляў наступных генаў: *HTR1A*, rs6295 (G/C); *BDNF*, rs6265 (G/A); *COMT*, rs4680 (G/A); *SKA2*, rs7208505 (C/T); *SLC6A4* (*5HTT*), rs25531 (T/C); *5HTR2A*, rs6313 (G/A); *TPH2*, rs4570625 (G/T); *TPH1*, rs1800532 (G/T).

Выяўлена статыстычна значная розніца ў частаце ўзнікнення генатыпаў і алеляў палімарфізму rs25531 гена *SLC6A4* (*5HTT*). Шанцы апынуцца ў групе самагубцаў гетэразіготнага генатыпу (T/C) былі ў 2,346 разы вышэй.

Пацверджана значэнне полімарфізму rs25531 гена *SLC6A4* (*5HTT*) для фарміравання суіцыдальных паводзін.

Ключавыя словы: малекулярна-генетычнае даследаванне, самагубства, генатып, полімарфізм, аллелі

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Introduction. Genetic studies of suicidal behavior are usually classified according to the severity of the intention to die, the method of committing suicide, its violent or non-violent type, mortality and personality components (impulsivity, aggressiveness) [1]. During this study, genetic factors associated with pronounced motivation to commit suicide were determined.

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

Materials and research methods. The study used the case-control method. The control group included 100 young men (18–27 years old), whose mental disorders were excluded. The control group included 30 people who committed highly traumatic methods of self-harm, motivated to commit suicide.

DNA was isolated using a NucleoSpin Blood kit (Macherey–Nagel, Germany) according to the protocol. Specific polymorphic sites of 9 genes were used as molecular targets. Information on target genes and polymorphic sites is presented in Tab. 1.

T a b l e 1. **Molecular targets and polymorphic sites selected for research**

No.	Target gene	Specific polymorphic site
1	*HTR1A*	rs6295 (G/C)
2	*BDNF*	rs6265 (G/A)
3	*COMT*	rs4680 (G/A)
4	*SKA2*	rs7208505 (C/T)
5	*5HTT* (*SLC6A4*)	rs25531 (T/C)
6	*5HTR2A*	rs6313 (G/A)
7	*TPH2*	rs4570625 (G/T)
8	*TPH1*	rs1800532 (G/T)
9	*5HTT* (*SLC6A4*)	rs4795541 (A/G)

Genotyping was performed using the allelic discrimination method based on real-time PCR data. The CFX 96 connect and CFX 96 Touch instruments (Bio-Rad, USA) were used for real-time PCR. Primary analysis of PCR data was performed using the software supplied with the instruments (Bio-Rad CFX Maestro 1.1, v. 4.1.2433.1219).

Primers and probes design was performed using the online services: Primer3 v. 0.4.0 (https://bioinfo.ut.ee/primer3-0.4.0/); OligoAnalyser (https://www.idtdna.com/calc/analyzer); Mfold web server (http://www.unafold.org/mfold/applications/dna-folding-form.php); NCBI database, the Homo sapiens assembly GRCh38.p13 (https://www.ncbi.nlm.nih.gov/genome/?term=Homo+sapiens). The sequences were visualized using the free software Ugene v.1.31 (http://ugene.net/ru/). The sequences of primers and probes are presented in Tab. 2.

T a b l e 2. **Sequences of primers and probes**

Names of primers and probes in the current research	Sequence 5′–3′	5′-end modification	3′-end modification
6265_F	TTGACATCATTGGCTGACAC		
6265_R	CGAACTTTCTGGTCCTCATC		
6265_W	TCGAA[LNA-C]A[LNA-C]GTGATAGAAGA	FAM	BHQ1
6265_M	T[LNA-C][LNA-G]AA[LNA-C]ACATGATAGAAGA	ROX	BHQ2
4680_F	CATCACCATCGAGATCAACC		
4680_R	TTTTTCCAGGTCTGACAACG		

End of Tab. 2

Names of primers and probes in the current research	Sequence 5′–3′	5′-end modification	3′-end modification
4680_W	CGCTGGCGTGAAGGACA	FAM	BHQ1
4680_M	TCGCTGGCATGAAGGACAA	ROX	BHQ2
6295_F	GAATGGGAAGGTGAACAGT		
6295_R	CGAGAACGGAGGTAGCTT		
6295_W	CGAGTGTGT[LNA-C]TTCGTTTTTAAA	FAM	BHQ1
6295_M	CGAGTG TGT[LNA-C]TTCCTTTTTAAA	ROX	BHQ2
7208505-F	CTGGGATGTGATGATGATTG		
7208505-R	TCCCTAACTGAAAGCAAAAC		
7208505-W	G[LNA-G]GATTGAAAAAACGGTAGTAT	FAM	BHQ1
7208505-M	G[LNA-G]G[LNA-A]TTGAAAAAATGGTAGTAT	ROX	BHQ2
25531_F	GGAGATCCTGGGAGAGGTG		
25531_R	CTCCTGCATCCCCCATTAT		
25531_t	GCAGGGGGGATGCTGGG	FAM	BHQ1
25531_c	GCAGGGGGGATGCCGG	HEX	BHQ1
6313_F	GTAAGGAGAGACACGACGGT		
6313_R	TGATGACACCAGGCTCTACAG		
6313_g	GTTAGCTTCTCCGGAGTTAAAGTC	FAM	BHQ1
6313_a	GTTAGCTTCTCC(LNA+A)GAGTTAAAGTC	HEX	BHQ1
4570625_F	GGCATCACAGGATTAAGAAGAAGC		
4570625_R	ACTCATTGACCAACTCCATTTTATGT		
4570625_g	TGCATGCACAAAATTAGAATATGTCAAGT	FAM	BHQ1
4570625_t	TGCATGCACAAAATTA(LNA+T)AATATGTCAAGT	HEX	BHQ1
1800532_F	TTTCCCCCACTGGAATACAA		
1800532_R	TTCCATGCTCTATATGTGTTAGCC		
1800532_g	CTCAGAATAGCAGCTAGCACCTAATAGG	FAM	BHQ1
1800532_t	CTCAGAATAGCAGCTA(LNA+T)CACCTAATAGG	HEX	BHQ1
4795541_F	GGGATGCTGGAAGGGCTG		
4795541_R	CTTCACCCCTCGCGGC		
4795541_a	GTGCAGGGG(LNA+A)GATGCTGG	FAM	BHQ1
4795541_g	GTGCAGGGGGGATGCTGG	HEX	BHQ1

Real-time PCR was performed using reagents produced by Primetech (Belarus). The final volume of the reaction mixture was 25 μL and contained all the necessary reagents at the following concentrations: 0.1 mM dNTP mixture, 2 mM $MgCl_2$ solution, 500 nM oligonucleotide primers, 250 nM fluorescently labeled probes, 1.25 units of thermostable Taq DNA polymerase with the appropriate buffer solution from the kit provided by the enzyme manufacturer. Thermal cycling: 95 °C – 3 minutes, then 45 cycles 95 °C – 10 seconds, 60 °C – 59 seconds.

The obtained results were processed by variational methods of mathematical statistics using the Microsoft Office 7.0 application package, the Statistic for Windows software package.

Research results. In genetic studies of serotonin biosynthesis, the main attention is paid to tryptophan hydroxylase (hereinafter *TPH*). *TPH* is an enzyme that is involved exclusively in the process of serotonin biosynthesis [2]. To date, two *TPH* isoforms have been identified, *TPH1* and *TPH2*, which have different tissue organization. The *TPH1* isoform is synthesized mainly in the walls of the duodenum, as well as in the liver, heart, lungs, kidneys and adrenal glands. Among the most intensively studied polymorphic markers of the *TPH1* gene, A218C and A779C are distinguished (both are localized within intron 7 and are in complete linkage disequilibrium). D. Nielsen et al. [3] report an association between these polymorphisms, the concentration of 5-hydroxyindoloacetic acid (hereinafter referred to as 5-OIAA) in CSF and suicidal attempts in violent offenders with alcohol dependence. J. Mann et al. [4] studied the possible association of the 218A allele with suicidal behavior in depression. They found that the A218C polymorphism was associated with impulsive aggression and anger traits that may predispose to suicide. However, the differences found are relatively small and statistically significant only for large samples.

In our study analysis of genotypes and alleles of the rs1800532 polymorphism of the *TPH1* gene revealed a slight increase in mutant type homozygotes (T/T) in the control group compared to suicide group, but this difference was statistically insignificant (Tab. 3).

T a b l e 3. **Frequency of occurrence of genotypes and alleles of rs1800532 polymorphism of *TPH1* gene**

Genotypes/alleles	Control group	Suicide group	χ^2	*p*	Odds ratios	OR (95 % CI)
G/G	50 (50)	17 (57)	1.126	0.570	0.765	0.336–1.739
G/T	32 (32)	10 (33)			0.941	0.395–2.241
T/T	18 (18)	3 (10)			1.976	0.540–7.230
G	132 (66)	44 (73.3)	0.135	0.287		
T	68 (68)	16 (26.7)				

The second isoform, *TPH2*, is characteristic exclusively for brain neurons. The *TPH2* gene is localized in the 12q21.1 region and consists of 12 exons and 11 introns. *TPH2* is expressed exclusively in the brain and plays an important role in the synthesis of serotonin in the brain. Z. Zhou et al. [5] performed an analysis of 10 single nucleotide polymorphisms (hereinafter referred to as SNPs) and analysis of the *TPH2* gene haplotypes, which showed a statistically significant association of this gene with completed suicide in a sample of persons of German descent. When comparing the frequencies of the genotypes and alleles of the rs4570625 polymorphism of the *TPH2* gene during our study, no statistically significant difference was observed in the control group and the suicide group (Tab. 4).

T a b l e 4. **Frequency of occurrence of genotypes and alleles of rs4570625 polymorphism of *TPH2* gene**

Genotypes/alleles	Control group	Suicide group	χ^2	*p*	Odds ratios	OR (95 % CI)
G/G	75 (75)	22 (73)	0.128	0.939	1.091	0.432–2.757
G/T	20 (20)	6 (20)			1.00	0.361–2.773
T/T	5 (5)	2 (7)			0.632	0.115–3.457
G	170 (85)	50 (83.3)	0.098	0.754		
T	30 (15)	10 (16.7)				

The *BDNF* gene encodes a protein of the same name, which is a neurotrophic factor in the brain. This protein is involved in the growth, maturation (differentiation) and maintenance of neurons. Currently about 30 pathogenic polymorphisms of the *BDNF* gene are known. Most of them are located in non-coding intron regions. The most common functional mutation of this gene is the missense variant rs6265 (p.196G-A, p.V66M). The 196G-A mutation in the *BDNF* gene shows connection to effects on general cognitive abilities, eating disorders, bipolar disorder, anxiety disorder, Alzheimer's and Parkinson's disease [4, 6]. The data for determining the frequency of occurrence of genotypes and alleles of the rs6265 polymorphism of the *BDNF* gene are presented in Tab. 5.

T a b l e 5. **Frequency of occurrence of genotypes and alleles of the rs6265 polymorphism of the *BDNF* gene**

Genotypes/alleles	Control group	Suicide group	χ^2	*p*	Odds ratios	OR (95 % CI)
G/G	76 (76)	20 (66.7)	2.177	0.337	1.583	0.652–3.844
G/A	18 (18)	9 (30)			0.512	0.202–1.302
A/A	6 (6)	1 (3.3)			1.851	0.214–16.01
G	170 (85)	49 (81.7)	0.386	0.535		
A	30 (15)	11 (18.3)				

The frequency of occurrence of the homozygous mutant genotype A/A is almost 2 times higher in the control group than in suicide group (difference are not statistically significant), however the frequencies of the alleles in both groups are approximately the same.

The *COMT* gene encodes catechol-O-methyltransferase (*COMT*), an enzyme involved in the breakdown of catecholamines, including dopamine, which is one of the most important neurotransmitters in the brain. *COMT* gene polymorphisms can disrupt the work of the dopaminergic system of the brain, especially in the prefrontal cortex, which leads to cognitive dysfunction and is considered one of the rea-

sons for the development of schizophrenia, bipolar disorder, and obsessive-compulsive disorder [7]. The data for determining the frequency of occurrence of genotypes and alleles of the rs4680 polymorphism of the *COMT* gene are presented in Tab. 6.

T a b l e 6. **Frequency of occurrence of genotypes and alleles polymorphism rs4680 of the *COMT* gene**

Genotypes/alleles	Control group	Suicide group	χ^2	*p*	Odds ratios	OR (95 % CI)
G/G	19 (19)	7 (23.3)	0.866	0.649	0.771	0.289–2.059
G/A	53 (53)	13 (43.3)			1.475	0.648–3.355
A/A	28 (28)	10 (33.3)			0.778	0.324–1.867
G	91 (45.5)	27 (45)	0.005	0.946		
A	109 (54,5)	33 (55)				

There were no significant differences in the frequency of occurrence of genotypes and alleles in both groups.

The *SKA2* gene is active in the prefrontal cortex where it reduces the brain's response to cortisol (a stress hormone), thus neutralizing the effects of negative emotions. Currently the *SKA2* gene is considered as one of the biological markers of suicidal behavior [8]. The data for determining the frequency of occurrence of genotypes and alleles of the rs7208505 polymorphism of the *SKA2* gene are presented in Tab. 7.

T a b l e 7. **Frequency of occurrence of genotypes and alleles of the rs7208505 polymorphism of the SKA 2 gene**

Genotypes/alleles	Control group	Suicide group	χ^2	*p*	Odds ratios	OR (95% CI)
C/C	16 (16)	6 (20)	0.393	0.822	0.762	0.269–2.160
C/T	49 (49)	15 (50)			0.961	0.425–2.173
T/T	35 (35)	9 (30)			1.256	0.520–3.036
C	81 (40.5)	27 (45)	0.385	0.536		
T	119 (59,5)	33 (55)				

There were no significant differences in the frequency of occurrence of genotypes and alleles between the control groups and suicide groups.

The *HTR1A* gene is located on the chromosomal region 5q11.2-q13. It was shown that the functional polymorphism –1019G/C (rs6295) in the promoter region controls the transcriptional activity of the gene and is associated with suicidal behavior and unipolar depression [9, 10]. Data on determining the frequency of genotypes and alleles of the rs6295 polymorphism of the *HTR1A* gene are presented in Tab. 8.

T a b l e 8. **Frequency of occurrence of genotypes and alleles of rs6295 polymorphism of the *HTR1A* gene**

Genotypes/alleles	Control group	Suicide group	χ^2	*p*	Odds ratios	OR (95 % CI)
G/G	26 (26)	4 (13.3)	2.131	0.345	2.284	0.728–7.167
G/C	24 (24)	9 (30)			0.737	0.298–1.823
C/C	50 (50)	17 (56.7)			0.765	0.336–1.739
G	76 (38)	17 (28)	1.877	0.171		
C	124 (62)	43 (72)				

As shown in Tab. 8, the frequency of occurrence of the G/G genotype in the control group was 2 times higher than in the suiside group (difference are not statistically significant). When comparing the frequency of occurrence of the G/G genotype in both groups, an odds ratio was 2.284 (the chance of committing suicide with the G/G genotype in the rs6295 polymorphism is 2 times higher than in individuals with a different genotype).

The *5HTR2A* gene encodes the serotonin receptor type 2A. The mammalian *5-HT2A* receptor is one of the subtypes of 5-HT2 receptors, a subfamily of serotonin receptors. It is a metabotropic G-protein coupled receptor. The receptor of this subtype (*5-HT2A*) is the main excitatory receptor subtype among all G-protein-coupled receptor subtypes for serotonin (5-HT). However receptors of the *5-HT2A* subtype can on the contrary exert an inhibitory effect in some areas of the brain such as the optic cortex and the

orbitofrontal cortex. Receptor activation triggers intracellular processes that affect the activity of other mediator systems – glutamate, dopamine, and GABA. The data for determining the frequency of occurrence of genotypes and alleles of the rs6313 polymorphism of the *5HTR2A* gene are presented in Tab. 9.

T a b l e 9. **Frequency of occurrence of genotypes and alleles of rs6313 polymorphism of the *5HTR2A* gene**

Genotypes/alleles	Control group	Suicide group	χ^2	*p*	Odds ratios	OR (95 % CI)
G/G	47 (47)	13 (43)	0.682	0.711	1.116	0.510–2.638
G/A	39 (39)	14 (47)			0.731	0.321–1.663
A/A	14 (14)	3 (10)			1.465	0.391–5.483
G	133 (66.5)	40 (66.7)	0.001	0.981		
A	67 (33.5)	20 (33.3)				

When comparing the frequencies of occurrence of genotypes and alleles in the control group and suicide group, no significant difference was observed.

The *SLC6A4* gene, abbreviated as SERT (Serotonin Transporter) or 5-HTT (5-HydroxyTriptamine Transporter), encodes an intracellular protein, a serotonin transporter or sodium-dependent serotonin transporter. The serotonin transporter belongs to the monoamine transporter family. Its physiological function is the reuptake and transport of serotonin from the synaptic cleft back to the presynaptic terminal that secreted it for reuse. This protein is a target of psychomotor stimulants such as amphetamines and cocaine and is a member of the sodium neurotransmitter symporter family. It has been shown that repeat length polymorphism in the promoter of this gene affects the rate of serotonin uptake. There are conflicting results in the literature on the possible effect that this polymorphism may have on behavior and depression [11, 12]. The data on determining the frequency of occurrence of genotypes and alleles of the rs25531 polymorphism of the *SLC6A4* (*5HTT*) gene are presented in Tab. 10.

T a b l e 10. **Frequency of occurrence of genotypes and alleles of rs25531 polymorphism of the *SLC6A4* (*5HTT*) gene**

Genotypes/alleles	Control group	Suicide group	χ^2	*p*	Odds ratios	OR (95 % CI)
T/T	37 (37)	18 (60)	5.298	0.071	0.392	0.170–0.903
T/C	61 (61)	12 (40)			2.346	1.019–5.4
C/C	2 (2)	0 (0)			–	–
T	135 (67.5)	48 (80)	3.46	0.063		
C	65 (32.5)	12 (20)				

When comparing the frequencies of occurrence of genotypes and alleles in the control group and suicide group, significant differences were noted. In the control group, the percentage of occurrence of the wild type genotype (T/T) is less than in the control group, and the frequency of occurrence of heterozygotes is higher respectively. The numerical value of OR (odds ratio) equal to 2.346 (confidence interval 95 % CI = 1.019–5.4) indicates that the chance of being in the suicide group with the carriage of a heterozygous genotype (T/C) is 2 times higher. That is, the risk factor is the heterozygous genotype (T/C).

We also studied the frequency of occurrence of genotypes and alleles of another polymorphism – rs4795541 of the *SLC6A4* (*5HTT*) gene (Tab. 11).

T a b l e 11. **Frequency of occurrence of genotypes and alleles of rs4795541 polymorphism of the *SLC6A4* (*5HTT*) gene**

Genotypes/alleles	Control group	Suicide group	χ^2	*p*	Odds ratios	OR (95 % CI)
A/A	5 (5)	2 (7)	0.997	0.608	0.737	0.136–4.006
A/G	66 (66)	22 (73)			0.706	0.284–1.752
G/G	29 (29)	6 (20)			1.634	0.605–4.412
A	76 (38)	26 (43.3)	0.551	0.459		
G	124 (62)	34 (56.7)				

No differences in the frequencies of all 3 genotypes and 2 alleles were found.

Discussion. As a result of the study, the frequencies of occurrence of genotypes and alleles of the following genes were analyzed: *HTR1A*, rs6295 (G/C); *BDNF*, (rs6265 (G/A); *COMT*, rs4680 (G/A); *SKA2*,

rs7208505 (C/T); *5HTT* (*SLC6A4*), rs25531 (T/C); *5HTR2A*, rs6313 (G/A); *TPH2*, rs4570625 (G/T); *TPH1*, rs1800532 (G/T). Statistically significant differences in the frequencies of genotypes and alleles of the rs25531 polymorphism of the *SLC6A4* (*5HTT*) gene were found. In the control group, the percentage of the occurrence of the wild-type genotype (T/T) was less than in the suicide group, and the frequency of occurrence of heterozygotes was correspondingly higher. The numerical value of OR (odds ratio) equal to 2.346 (confidence interval 95 % CI) = 1.019–5.4) suggests that the likelihood of falling into the suicide group in the presence of heterozygous genotype (T/C) is 2.346 times higher. Thus, it was found that the frequency of occurrence of the heterozygous genotype (T/C) corresponds to the frequency of occurrence of this genotype in the group of persons prone to true suicide, which is consistent with the data of previous studies [1, 13]. The significance of the allele polymorphisms of the genes: *HTR1A*, rs6295 (G/C); *BDNF*, (rs6265 (G/A); *COMT*, rs4680 (G/A); *SKA2*, rs7208505 (C/T); *5HTT* (*SLC6A4*), rs25531 (T/C); *5HTR2A*, rs6313 (G/A); *TPH2*, rs4570625 (G/T); *TPH1*, rs1800532 (G/T), which are regarded as possible genetic factors of suicidal behavior however it has not been confirmed. This emphasizes the complexity of this problem, despite a long period (more than 10 years) of research, has not yet found its solution.

Conclusion. This study has confirmed the possibility of using molecular genetic studies to identify individuals prone to suicidal behavior.

Conflict of interests. The authors declare no conflict of interests.

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