Scientific Notes of Crimean V. I. Vernadsky Federal University
Biology. Chemistry. Vol. 7 (73). 2021. No 4. P. 69–78.

UDK 575.21

VIRTUAL SCREENING SNP OF GENES ASSOCIATED WITH THE RISK OF USING PSYCHOACTIVE SUBSTANCES TAKING INTO ACCOUNT DIFFERENT PHENOTYPE SIGNS

Krylov P. A.[1], Gerasimova E. O.[1], Shatyr Y. A.[1], Mulik A. B.[2]

[1]Volgograd State University, Volgograd, Russian Federation
[2]Federal State-Financed Institution Golikov Research Clinical Center of Toxicology under the Federal Medical Biological Agency, Saint Petersburg, Russian Federation
E-mail: krylov.pavel@volsu.ru

The virtual screening of SNP was performed using an automated program that automatically searched for articles and generated a list that included polymorphisms associated with the risk of substance use and various phenotypic traits. The screening found over 800 publications describing the relationship of addictions to psychoactive substances associated with various phenotypic traits of a person. To assess these relationships, 19 most common polymorphisms were selected. As a result of the analysis, it was revealed that in a number of cases the effect of one or another polymorphism on the phenotypic traits of a person has no proven clinical significance, is localized in possible regulatory sites and does not lead to structural and functional changes in proteins. Out of 19 polymorphisms, 7 were selected: rs6579845, rs1360780, rs16965628, rs1800497, rs1789891, rs6277, and rs4680 as the most likely candidates for the role of key SNPs associated with phenotype parameters characteristic of a psychoactive substance user.
Keywords: PMC, SNP, psychoactive substances, human phenotype, virtual screening SNP, data bases SNP.

INTRODUCTION

The biological predisposition to drug addiction, alcoholism and tobacco smoking is due to a number of specific manifestations of the neurochemical functions of the brain, provoking the development of mental and physical dependence on psychoactive substances (PAS). These manifestations, in turn, are a consequence of the implementation of the individual genetic program of human ontogenesis. Currently, a set of genes is known for which a convincing confirmation of their connection with the emergence of a narcotic drug has been obtained and published [1], alcoholic [2, 3] and tobacco [4, 5] dependencies.

At the same time, the role of phenotypic factors in the formation of the risk of the demand for PAS is known. A number of studies confirm the presence of links between the somatotype and psychological qualities of a person with the consumption of, first of all, "legal" PAS [6, 7]. Previously performed own studies substantiated the influence of psychophysiological status on the development of alcohol and tobacco dependence in humans. It was determined that an increased propensity to consume alcohol and smoke tobacco is associated with a high level of general nonspecific reactivity of the body [8, 9]. Further study of the mechanisms of the formation of a person's tendency to the demand for

PAS requires the specification of the most probable genes and their polymorphisms, which determine the phenotypic signs of the manifestation of deviant forms of behavior that form the risk of the studied addictions.

The search and analysis of polymorphisms can be divided into two approaches. The first approach involves the experimental production of mDNA or mRNA, their sequencing and assembly of the genome (genes), followed by decoding and entering the results into the dbSNP [10, 11]. The second approach is bioinformatic, which is an automated virtual screening of SNP databases and the identification of those polymorphisms that have not been studied or could be of interest for study for solving problems in various fields of science. In this regard, we chose the second approach, since there is a lot of data on polymorphisms and their number is constantly increasing, and manual analysis requires a lot of time.

MATERIALS AND METHODS

The algorithm used was developed in the form of a script written in the Pythonv programming language. 3.6.5 (Python Software Foundation, USA) in PyCharm environment (USA) [12]. The following plug-in libraries and modules were used to develop the algorithm: the Requests v.2.24.0 library was used to implement the request; for searching and selecting information from database sites – library Beautifulsoup4 v.4.9.1. [13]. The script was executed on the command line, and saved to a Microsoft Excel (Microsoft, USA). The databases Pub Med Central (National Institutes of Health's National Library of Medicine, USA) and dbSNP (National Center for Biotechnology Information, USA).

The search and work on the study of SNPs took place in two main stages. The first stage included a search for publications in Pub Med Central (National Institutes of Health's National Library of Medicine, USA) that mention SNP and its relationship with phenotypic traits, as well as the use of surfactants using an algorithm [12]. The following synonymous construct was used for the search: [Psychoactive substances or alcohol or tobacco or smoking or drugs] and [Pain sensitivity or reactivity of the body or body mass index or height or weight or excitability or anxiety or cyclothymic or aggressive or depressive or extraverted or adventurous or masculine or activity or hyperthyness or shyness or emotiveness or empathy or exaltation] and [human or man or woman] and SNP. After that, in the publications found, 2 experts in this field analyzed and identified SNP associated with the human phenotype and the use of surfactants.

At the second stage, the analysis of the found SNP was carried out, which in the future can be verified experimentally. The analysis was carried out according to the 2nd stage of the algorithm [12]: SNP ID, gene: position in the chromosome (-s), allele, clinical significance, consequence, global frequency of minor alleles (MAF), phenotypic variation and/or psychoactive drug.

RESULTS AND DISCUSSION

As a result of the work at the first stage, as a result of a search using synonymous constructs, 834 articles were found. As a result of the operation of the algorithm, a table

was generated that includes: the title of the article, a link to PubMedCentralID and the phenotypic traits and / or PAS (an example is in Table 1).

Table 1

Article title, link in PubMedCentral ID and phenotypic traits and / or PAS

Name	PubMedCentral ID	Phenotypic variation and/or Psychoactive drug
GWAS and network analysis of co-occurring nicotine and alcohol dependence identifies significantly associated alleles and network	30488612	**alcohol dependence co-occurring nicotine dependence**, genome-wide association studies, network analysis, pleiotropy

Some publications were excluded from the analysis if they did not contain any data on the relationship of phenotypic traits and surfactants with SNP.

As a result, after analyzing all publications, experts selected 19 SNP for further work (Table 2).

During the analysis, three SNP of the GM2A gene (ganglioside activator) were found. Polymorphism rs6579845 was found in people addicted to alcohol and nicotine [11]. This polymorphism leads to a nucleotide change in the intron and has no proven clinical manifestations at the moment. The other two polymorphisms, rs12516391 and rs3806953, do not lead to negative consequences and are mainly involved only in the regulation of translation of the GM2A protein. In connection with the above, only rs6579845 can be used as a genetic marker to detect the presence of alcohol or nicotine addiction and phenotypic traits associated with them.

As a result of the expression of the FKBP5 gene, a part of the complex with the glucocorticoid receptor is formed, which is involved in modulating the expression of glucocorticoid hormones.

The selected SNP of this gene are associated with phenotypic traits formed by various factors. For example, the relationship of rs1360780 with the use of antidepressants [14, 15], mental illness [16], changes in body mass index in people of different sex and age [17] and other factors (about 166 publications). Polymorphisms rs1360780 and rs9470080 are localized in the intron, and rs3800373 is involved in the regulation of translation; therefore, most likely, these polymorphisms do not directly change the protein, but regulate its expression and possibly participate in alternative splicing. However, clinical manifestations are either absent or not proven according to the ClinVar database.

The rs16965628 polymorphism is associated with the serotonin transporter gene SLC6A4, which ensures the availability of serotonin in the synaptic cleft, which is inhibited by the use of drugs such as cocaine. In recent studies, it was found that the above polymorphism is associated with cocaine and opiate addiction [18, 19]. Also, rs16965628 is associated with the development of mental diseases, such as obsessive-compulsive disorder [20]. All conducted studies of rs16965628 had a small sample and therefore cannot be considered reliable.

Table 2

SNP associated with the risk of substance use and human phenotypic traits

SNP id	Gene: position	Allele	Clinical significance	Consequence	MAF	Phenotypic variation and/or Psychoactive drug
1	2	3	4	5	6	7
rs6579845	GM2A:chr5: 151262704	A>G	-	Intron variant	G=0.28 A=0.39	alcohol and nicotine addiction [11]
rs12516391	GM2A:chr5: 151269445	A>G	benign	3 Prime UTR variant	G=0.22 A=0.38	
rs3806953	GM2A:chr5: 151269317	C>G /C>T	benign	3 Prime UTR variant	T=0.22 C=0.38	
rs1360780	FKBP5:chr6: 35639794	T>A /T>C	drug response	Intron variant	T=0.34	depression [14, 15] body mass index [17] psychic disease [16]
rs3800373	FKBP5:chr6: 35574699	C>A /C>G	-	3 Prime UTR variant	C=0.33	
rs9470080	FKBP:chr6:35678658	T>A /T>C	-	Intron variant	T=0.37	
rs16965628	SLC6A4:chr17:30228407	G>C	-	Intron variant	C=0.14 G=0.39	drug addiction [19] psychic disease [20]
rs1800497	ANKK1:chr11:113400106	G>A	drug response	Missense variant	A=0.27	alcohol [21] and antidepressants [22, 23] addiction, body mass index [24]
rs1229984	ADH1B:chr4:99318162	T>C /T>G	drug respons, not proved	Missense variant	T=0.06 C=0.31	alcohol [25, 28, 29] and drug [27] addiction
rs1789891	ADH1B/1C: chr4:99329262	C>A /C>G	-	Missense variant	A=0.15 C=0.43	
rs2835859	KCNJ6:chr21:37645860	T>C /T>G	-	Intron variant	C=0.15 T=0.42	nicotine addiction [30]
rs6277	DRD2:chr11: 113412737	G>A	benign	Synonymous variant	A=0.41	depression [31, 32]
rs17818902	FTO:chr16:53837894	T>G	-	Intron variant	G=0.27 T=0.39	obesity [33]

Table continuation 2

1	2	3	4	5	6	7
rs1611115	DBH:chr9:133635393	T>A /T>C /T>G	Benign, not proved	Upstream variant	T=0.21	nervous system diseases [35, 36], drug addiction [37]
rs2399496	DRD3:chr3:114127166	T>A /T>G	-	Downstream variant	A=0.45 T=0.40	depression and nicotine addiction [39]
rs4680	COMT:chr22:19963748	G>A	drug response	Missense variant	A=0.48 G=0.45	psychic disease, depression, schizophrenia [40], alcohol addiction and aggression [21]
rs4532	DRD1:chr5:175443147	C>G /C>T	Benign, not proved	5 Prime UTR variant	C=0.32	impulsivity [21], psychic disease [42], psychoactive drug addiction [41]
rs6280	DRD3:chr3:114171968	C>T	Benign/ Likely benign	Missense variant	C=0.47 T=0.45	psychic disease [44], alcohol [21] and nicotine [45] addiction
rs6923492	GRM1:chr6:146434188	T>A /T>C	Benign	Missense variant	T=0.47 C=0.47	psychic disease [46]

The ANKK1 gene is involved in the regulation of dopamine synthesis, which means it is one of the links involved in the modulation of the dopaminergic system. The rs1800497 polymorphism results in an amino acid substitution that affects the activity of the Ser / Thr family protein kinase. Currently, it is known that there are a large number of genetic disorders in the dopaminergic system (over 300 publications), which have a strong influence on the formation of phenotypic traits associated with deviant behaviors in both men and women in response to, for example, alcohol consumption [21], psychoactive substances in mental illness [22, 23] and overweight [24].

Alcohol dehydrogenase IB (ADH1B) beta polypeptide gene polymorphisms are well studied and are directly related to the risk of alcohol consumption and its metabolism in the body. Currently, most studies are aimed at identifying or confirming the relationship of the rs1229984 and rs1789891 polymorphisms not only with the risk of developing alcoholic [25, 26] and narcotic [27] dependences, but also other human diseases, for example, collateral cancer [28], as well as with the influence of the environment on the realization of phenotypic manifestations formed in individuals with the presence of this polymorphism [29].

The rs2835859 polymorphism was found in the KCNJ6 gene, which is responsible for the translation of GIRK2, a subunit of the G-protein-coupled internal rectifying potassium channel (the so-called GIRK). The results of the study indicate that rs2835859 can serve as an indicator predicting sensitivity to anesthesia and nicotine addiction [30].

The DRD2 gene, which is responsible for the dopamine D2 receptor, has the rs6277 polymorphism. By its type, polymorphism is benign / conditionally benign. Polymorphism can lead to an increase in the propensity for psychosis. Allele C rs6277 DRD2 was associated with higher levels of psychotic-like experiences [31] It was assumed that polymorphism is associated with behavior in solving simple / complex problems. However, no effect of DRD2 genotypes was found [32].

The FTO gene encodes the FTO protein involved in energy metabolism and affecting metabolism in general. Currently, there are studies aimed at finding links between rs17818902 and obesity [33], but also with smoking, although no such dependence was found [34]. The polymorphism rs17818902 is in the intron and has no clinical manifestations according to the ClinVar database. It is unlikely that this polymorphism will determine smoking status, like the FTO gene itself.

The rs1611115 polymorphism is associated with the DBH gene, which encodes the dopamine beta-hydroxylase enzyme. This enzyme catalyzes the conversion of dopamine to norepinephrine. Numerous studies of the dependence of various diseases have been associated with this polymorphism. So it is more likely that this polymorphism can be considered a genetic marker of Alzheimer's disease [35, 36]. It was also found that the presence of rs1611115 reduced the total use of cocaine with the use of disulfiram [37]. No association with Parkinson's disease was found [38]. The reliability has not been confirmed by the "ClinVar" database.

In a study [39], the rs2399496 polymorphism, located 1.5 kb downstream of the DRD3 dopamine receptor gene, showed a suggestive association with major depressive disorder and a significant association with concomitant incidence of nicotine addiction. This polymorphism is poorly understood and has no clinical manifestations according to the ClinVar database.

COMT (catechol-O-methyltransferase) is a gene responsible for the translation of an enzyme that deactivates dopamine. The rs4680 (A; A) polymorphism results in decreased enzymatic activity and increased dopamine levels. Polymorphism of the type (G; G) is associated with a tendency to use cannabioids in adolescence and schizotypal manifestations in adulthood. The severity is lost with polymorphism (G; A), weakly expressed with (A; A). Moreover, this polymorphism affects the development of schizophrenia [40], depression and dependence on the use of psychoactive substances. Also, when alcoholic beverages are abused, it affects aggressiveness and impulsivity [21].

In the rs4532 polymorphism of the DRD1 gene, which encodes the dopamine receptor D1, a receptor for dopamine coupled with G-proteins, stimulating adenylate cyclase and activating AMP-dependent kinases, a significant association with impulsivity was revealed [21]. In several studies, the rs4532 polymorphism in DRD1 is considered as a potential pharmacogenomic marker of response to antipsychotic drug treatment [41], for example, prizophrenia [42]. It has also been established that the presence of the rs4532 polymorphism when taking antipsychotics does not lead to weight gain [43]. Clinical manifestations are benign according to the "ClinVar" database.

The rs6280 polymorphism is associated with the DRD3 gene, which encodes the D3 dopamine receptor. This receptor inhibits adenylate cyclase. The type of polymorphism is a missense mutation that leads to the formation of another amino acid. Numerous studies of the dependence of various diseases have been associated with this polymorphism. A significant

association was found between the DRD3 SNP rs6280 and scores on the obsessive-compulsive alcohol use scale [21]. Found a relationship in this polymorphism with schizophrenia in women [44]. Ser9/Gly single nucleotide polymorphism (SNP; rs6280) leads to D3R variants that have been identified and associated with smoking in humans [45]. SNP Ser9/Gly D3R corresponds to the substitution of serine for glycine at position 9 of the N-terminal extracellular domain. Clinical manifestations are benign in the "ClinVar" database.

The rs6923492 polymorphism belongs to the GRM1 gene (glutamate metabotropic receptor 1). This gene encodes the metabotropic glutamate receptor, which functions by activating phospholipase C. This gene can be associated with many disease conditions, including schizophrenia, bipolar disorder, depression, and breast cancer. The polymorphism itself changes the amino acid from Ser to Thr or Pro. It can also affect the development of autosomal recessive spinocerebellar ataxia-13 (SCAR13) according to ClinVar, attention deficit / hyperactivity disorder (ADHD) [46].

It should be noted that all the above polymorphisms are described for different populations of people, different sex, age and place of residence. In most cases, the effect of one or another polymorphism on the phenotypic traits of a person has no proven clinical significance. It is also not unimportant that some of the polymorphisms are localized in introns or regulatory regions; therefore, it is difficult to assert about their direct influence on the change in the functional activity of proteins encoded by these genes.

CONCLUSIONS

Virtual screening of SNP of genes associated with the risk of substance use showed that a variety of polymorphisms leads to the development of various phenotypic traits, caused in most cases by alcohol and nicotine addiction. The studied polymorphisms lead to the development of various mental illnesses and metabolic disorders of the body.

For further experimental verification of the effect of polymorphisms on human phenotypic traits and population characteristics of humans, the following SNPs were selected: rs6579845, rs1360780, rs16965628, rs1800497, rs1789891, rs6277, and rs4680. These polymorphisms are associated with all types of addiction to psychoactive substances, and at the moment they have partially or completely proven phenotypic traits in humans.

Acknowledgments:The reported study was funded by RFBR according to the research project № 20-013-00145 "Mechanisms for the complex influence of environmental factors on the consumption of psychoactive substances by the population of local territories of the Russian Federation".

References

1. Donaldson K., Demers L., Taylor K., Lopez J. and Chang S. Multi-variant genetic panel for genetic risk of opioid addiction. *Ann Clin Lab Sci*., **47(4)**, 452 (2017).
2. van der Zwaluw C. S., Engels R. C., Buitelaar J., Verkes R. J., Franke B. and Scholte R. H. Polymorphisms in the dopamine transporter gene (SLC6A3/DAT1) and alcohol dependence in humans: a systematic review. *Pharmacogenomics*, **10(5)**, 853 (2009).
3. Lai D., Wetherill L., Bertelsen S., Carey C. E., Kamarajan C., Kapoor M., Meyers J. L., Anokhin A. P., Bennett D. A., Bucholz K. K., Chang K. K., De Jager P. L., Dick D. M., Hesselbrock V., Kramer J., Kuperman S., Nurnberger J. I., Jr Raj T., Schuckit M., Scott D. M., Taylor R. E., Tischfield J.,

Hariri A. R., Edenberg H. J., Agrawal A., Bogdan R., Porjesz B., Goate A. M. and Foroud T. Genome-wide association studies of alcohol dependence, DSM-IV criterion count and individual criteria. *Genes, brain, and behavior*, **18(6)**, e12579 (2019).

4. Sullivan P. F. and Kendler K. S. The genetic epidemiology of smoking, *Nicotine Tob Res*., **1,** Suppl 2, S51 discussion, S69 (1999).
5. Uhl G. R., Drgon T., Li C. Y., Johnson C. and Liu Q. R. Smoking and smoking cessation in disadvantaged women: assessing genetic contributions. *Drug Alcohol Depend*. **104,** Suppl 1, S58 (2009).
6. Murphy C. M., Janssen T., Colby S. M. and Jackson K. M. Low self-esteem for physical appearance mediates the effect of body mass index on smoking Initiation among adolescents. *J. Pediatr Psychol*., **44(2)**, 197 (2019).
7. Lastovetsky A. G., Timoshilov V. I. and Bobrik Yu. V. Risk factors of drug abuse among young people: analytical review and expert evaluation. *Tavricheskiy mediko-biologicheskiy vestnik*, **22(1)**, 129 (2019).
8. Mulik A. B., Bulatetsky S. V., Ulesikova I. V., Mulik I. G., Nazarova E. V. and Shatyr Y. A. Optimization of evaluation human tendecy for alcohol consumption. *I P Pavlov Russian Medical Biological Herald*, **24(4)**, 6 (2016).
9. Mulik A. B., Postnova M. V., Mulik I. G., Ulesikova I. V. and Shatyr Y. A. Development of a system for the comprehensive assessment of a person's propensity to tobacco smoking. *Narcology*, **16(7)**, 85 (2017).
10. Mori Y., Saito T., Chang S. H., Kobayashi H., Ladel C. H., Guehring H., Chung U. I. and Kawaguchi H. Identification of fibroblast growth factor-18 as a molecule to protect adult articular cartilage by gene expression profiling. *J Biol Chem*., **289(14)**, 10192 (2014).
11. Xiang B., Yang B. Z., Zhou H., Kranzler H. and Gelernter J. GWAS and network analysis of co-occurring nicotine and alcohol dependence identifies significantly associated alleles and network. *Am J Med Genet B Neuropsychiatr Genet*., **180(1)**, 3 (2019).
12. Krylov P. A., Gerasimova E. O., Shatyr Yu. A., Mulik A. B. and Novochadov V. V., Development the algorithm for virtual screening of protein polymorphisms affecting their structural and functional properties. *European Journal of Molecular Biotechnology*, 8(1), 35 (2020).
13. Plotnikov A., Shcheludyakov A., Cherdantsev V., Bochkarev A. and Zagoruiko I. Data on post bank customer reviews from web. *Data Brief*., **32**, 106152 (2020).
14. Binder E. B., Salyakina D., Lichtner P., Wochnik G. M., Ising M., Pütz B., Papiol S., Seaman S., Lucae S., Kohli M. A., Nickel T., Künzel H. E., Fuchs B., Majer M., Pfennig A., Kern N., Brunner J., Modell S., Baghai T., Deiml T., Zill P., Bondy B., Rupprecht R., Messer T., Köhnlein O., Dabitz H., Brückl T., Müller N., Pfister H., Lieb R., Mueller J. C., Lõhmussaar E., Strom T. M., Bettecken T., Meitinger T., Uhr M., Rein T., Holsboer F. and Muller-Myhsok B. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet*., **36(12)**, 1319 (2004).
15. Lekman M., Laje G., Charney D., Rush A.J., Wilson A.F., Sorant A.J., Lipsky R., Wisniewski S.R., Manji H., McMahon F.J. and Paddock S. The FKBP5-gene in depression and treatment response-an association study in the sequenced treatment alternatives to relieve depression (STAR*D) cohort. *Biological psychiatry*, **63(12)**, 1103 (2008).
16. Willour V. L., Chen H., Toolan J., Belmonte P., Cutler D. J., Goes F. S., Zandi P. P., Lee R. S., MacKinnon D. F., Mondimore F. M., Schweizer B., Bipolar Disorder Phenome Group; NIMH Genetics Initiative Bipolar Disorder Consortium, DePaulo J. R. Jr, Gershon E. S., McMahon F. J. and Potash J. B. Family-based association of FKBP5 in bipolar disorder. *Mol Psychiatry*. **14(3)**, 261 (2009).
17. Peña E., Caixàs A., Arenas C., Rigla M., Crivillés S., Cardoner N. and Rosa A. Role of the FKBP5 polymorphism rs1360780, age, sex, and type of surgery in weight loss after bariatric surgery: a follow-up study. *Surgery for obesity and related diseases*, **16(4)**, 581 (2020).
18. Enoch M. A., Gorodetsky E., Hodgkinson C., Roy A. and Goldman D. Functional genetic variants that increase synaptic serotonin and 5-HT3 receptor sensitivity predict alcohol and drug dependence. *Molecular psychiatry*, **16(11)**, 1139 (2011).
19. Levran O., Peles E., Randesi M., Correa da Rosa J., Ott J., Rotrosen J., Adelson M. and Kreek M. J. Susceptibility loci for heroin and cocaine addiction in the serotonergic and adrenergic pathways in populations of different ancestry. *Pharmacogenomics*, **16(12)**, 1329 (2015).

20. Grünblatt E., Marinova Z., Roth A., Gardini E., Ball J., Geissler J., Wojdacz T. K., Romanos M. and Walitza S. Combining genetic and epigenetic parameters of the serotonin transporter gene in obsessive-compulsive disorder. *Journal of psychiatric research*, **96**, 209 (2018).
21. Park C. I., Kim H. W., Hwang S. S., Kang J. I. and Kim S. J. Influence of dopamine-related genes on craving, impulsivity, and aggressiveness in Korean males with alcohol use disorder. *European archives of psychiatry and clinical neuroscience*, **271(5)**, 865 (2021).
22. López-Rodríguez R., Cabaleiro T., Ochoa D., Román M., Borobia A. M., Carcas A. J., Ayuso C., Novalbos J. and Abad-Santos F. Pharmacodynamic genetic variants related to antipsychotic adverse reactions in healthy volunteers. *Pharmacogenomics*, **14(10)**, 1203 (2013).
23. Sukasem C., Hongkaew Y., Ngamsamut N., Puangpetch A., Vanwong N., Chamnanphon M., Chamkrachchangpada B., Sinrachatanant A. and Limsila P. Impact of pharmacogenetic markers of CYP2D6 and DRD2 on prolactin response in risperidone-treated thai children and adolescents with autism spectrum disorders. *Journal of clinical psychopharmacology*, **36(2)**, 141 (2016).
24. Aliasghari F., Nazm S. A., Yasari S., Mahdavi R. and Bonyadi M. Associations of the ANKK1 and DRD2 gene polymorphisms with overweight, obesity and hedonic hunger among women from the Northwest of Iran. *Eating and weight disorders:EWD*, **26(1)**, 305 (2021).
25. Yokoyama A., Omori T. and Yokoyama T. Risk factors for esophageal iodine-unstained lesions and changing trends among Japanese alcohol-dependent men (2003-2018). *Cancer science*, **112(2)**, 734 (2021).
26. Oniszczenko W., Rybakowski J. K., Dragan W. Ł., Grzywacz A. and Samochowiec J. The ADH gene cluster SNP rs1789891 and temperamental dimensions in patients with alcohol dependence and affective disorders. *Scandinavian journal of psychology*, **56(4)**, 420 (2015).
27. Demers C. H., Bogdan R. and Agrawal A. The Genetics, Neurogenetics and Pharmacogenetics of Addiction. *Current behavioral neuroscience reports*, **1(1)**, 33 (2014).
28. Yokoyama A., Taniki N., Nakamoto N., Tomita K., Hara S., Mizukami T., Maruyama K., and Yokoyama T. Associations among liver disease, serum lipid profile, body mass index, ketonuria, meal skipping, and the alcohol dehydrogenase-1B and aldehyde dehydrogenase-2 genotypes in Japanese men with alcohol dependence. *Hepatology research*, **50(5)**, 565 (2020).
29. Clarke T. K., Adams M. J., Howard D. M., Xia C., Davies G., Hayward C., Campbell A., Padmanabhan S., Smith B. H., Murray A., Porteous D., Deary I. J. and McIntosh A. M. Genetic and shared couple environmental contributions to smoking and alcohol use in the UK population. *Molecular psychiatry*, **26(8)**, 4344 (2021).
30. Nishizawa D., Fukuda K., Kasai S., Ogai Y., Hasegawa J., Sato N., Yamada H., Tanioka F., Sugimura H., Hayashida M. and Ikeda K. Association between KCNJ6 (GIRK2) gene polymorphism rs2835859 and post-operative analgesia, pain sensitivity, and nicotine dependence. *Journal of pharmacological sciences*, **126(3)**, 253 (2014).
31. Kotowicz K., Frydecka D., Gawęda Ł., Prochwicz K., Kłosowska J., Rymaszewska J., Samochowiec A., Samochowiec J., Szczygieł K., Pawlak-Adamska E., Szmida E., Cechnicki A. and Misiak B. Effects of traumatic life events, cognitive biases and variation in dopaminergic genes on psychosis proneness. *Early intervention in psychiatry*, **15(2)**, 248 (2021).
32. Zink N., Bensmann W., Arning L., Colzato L.S., Stock A. K. and Beste C. The role of DRD1 and DRD2 receptors for response selection under varying complexity levels: implications for metacontrol processes. *The international journal of neuropsychopharmacology*, **22(12)**, 747 (2019).
33. Srivastava A, Mittal B, Prakash J, Srivastava P, Srivastava N. and Srivastava N. A multianalytical approach to evaluate the association of 55 SNPs in 28 genes with obesity risk in North Indian adults. *Am J Hum Biol*., **29(2)**, (2017).
34. Hubacek J. A., Dlouha D., Lanska V. and Adamkova V. Lack of an association between three tagging SNPs within the FTO gene and smoking behavior. *Nicotine Tob Res*., **14(8)**, 998 (2012).
35. Babić Leko M., Nikolac Perković M., Klepac N., Švob Štrac D., Borovečki F., Pivac N., Hof P. R. and Šimić G. Relationships of cerebrospinal fluid Alzheimer's disease biomarkers and COMT, DBH, and MAOB single nucleotide polymorphisms. *J. Alzheimers Dis*., **73(1)**, 135 (2020).
36. Belbin O., Morgan K., Medway C., Warden D., Cortina-Borja M., van Duijn C. M., Adams H. H. H., Frank-Garcia A., Brookes K., Sánchez-Juan P., Alvarez V., Heun R., Kölsch H., Coto E., Kehoe P. G., Rodriguez-Rodriguez E., Bullido M. J., Ikram M. A., Smith A. D. and Lehmann D. J. The epistasis

project: A multi-cohort study of the effects of BDNF, DBH, and SORT1 epistasis on Alzheimer's disease risk. *J Alzheimers Dis*., **68(4)**, 1535 (2019).
37. Zhang X., Nielsen D. A., Domingo C. B., Shorter D. I., Nielsen E. M. and Kosten T. R. Pharmacogenetics of dopamine β-Hydroxylase in cocaine dependence therapy with doxazosin. *Addict Biol.*, **24(3)**, 531 (2019).
38. Chen Y., Ou R., Zhang L., Gu X., Yuan X., Wei Q. Q., Cao B., Zhao B., Wu Y. and Shang H. Contribution of five functional loci of dopamine metabolism-related genes to Parkinson's disease and multiple system atrophy in a Chinese population. *Front Neurosci*., **14**, 889 (2020).
39. Korhonen T., Loukola A., Wedenoja J., Nyman E., Latvala A., Broms U., Häppölä A., Paunio T., Schrage A. J., Vink J. M., Mbarek H., Boomsma D. I., Penninx B. W., Pergadia M. L., Madden P. A. and Kaprio J. Role of nicotine dependence in the association between the dopamine receptor gene DRD3 and major depressive disorder. *PLoS One*., **9(6)**, e98199 (2014).
40. Kogure M., Kanahara N., Miyazawa A., Oishi K., Nakata Y., Oda Y. and Iyo M. Interacting roles of COMT and GAD1 genes in patients with treatment-resistant schizophrenia: a genetic association study of schizophrenia patients and healthy controls. *J Mol Neurosci*., **71(12)**, 2575 (2021).
41. De Matos L. P., Santana C. V. and Souza R. P. Meta-analysis of dopamine receptor D1 rs4532 polymorphism and susceptibility to antipsychotic treatment response. *Psychiatry Res*., **229(1-2)**, 586 (2015).
42. Ota V. K., Spíndola L. N., Gadelha A., dos Santos Filho A. F., Santoro M. L., Christofolini D. M., Bellucco F. T., Ribeiro-dos-Santos Â. K., Santos S., Mari Jde J., Melaragno M. I., Bressan R. A., Smith Mde A. and Belangero S. I. DRD1 rs4532 polymorphism: a potential pharmacogenomic marker for treatment response to antipsychotic drugs. *Schizophr Res.*, **142(1–3)**, 206 (2012).
43. Luo C., Liu J., Wang X., Mao X., Zhou H. and Liu Z. Pharmacogenetic correlates of antipsychotic-induced weight gain in the Chinese population. *Neurosci Bull*., **35(3)**, 561 (2019).
44. Morozova A., Zorkina Y., Pavlov K., Pavlova O., Storozheva Z., Zubkov E., Zakharova N., Karpenko O., Reznik A., Chekhonin V. and Kostyuk G. Association of rs4680 COMT, rs6280 DRD3, and rs7322347 5HT2A with clinical features of Youth-Onset schizophrenia. *Front Psychiatry*, **12**, 830 (2019).
45. Chukwueke C. C., Kowalczyk W. J., Di Ciano P., Gendy M., Taylor R., Heishman S. J. and Le Foll B. Exploring the role of the Ser9Gly (rs6280) Dopamine D3 receptor polymorphism in nicotine reinforcement and cue-elicited craving. *Scientific reports*, **10(1)**, 4085 (2020).
46. Waltes R., Freitag C. M., Herlt T., Lempp T., Seitz C., Palmason H., Meyer J. and Chiocchetti A. G. Impact of autism-associated genetic variants in interaction with environmental factors on ADHD comorbidities: an exploratory pilot study. *Journal of neural transmission*, **126(12)**, 1679 (2019).

Крылов П. А. Виртуальный скрининг SNP генов, ассоциированных с фенотипическими признаками, связанными с риском употребления психоактивных веществ / П. А. Крылов, Е. О. Герасимова, Ю. А. Шатыр, А. Б. Мулик // Ученые записки Крымского федерального университета им. В. И. Вернадского. Биология, химия. – 2021. – Т. 7 (73), №4. – С. 69–78.

Виртуальный скрининг SNP проводился с использованием программы, которая выполняла поиск статей, включающий SNP, связанные с риском употребления психоактивных веществ и различными фенотипическими признаками. В ходе скрининга было обнаружено свыше 800 публикаций, описывающих взаимосвязь зависимости от психоактивных веществ и различными фенотипическими чертами человека. В результате анализа было выявлено, что в ряде случаев влияние того или иного SNP на фенотипические признаки человека не имеет доказанного клинического значения, локализуется в возможных регуляторных участках и не приводит к структурным и функциональным изменениям белков. Из 19 SNP было выбрано 7: rs6579845, rs1360780, rs16965628, rs1800497, rs1789891, rs6277 и rs4680 в качестве наиболее вероятных кандидатов на роль ключевых SNP, связанных с параметрами фенотипа, характерными для потребителя психоактивных веществ.

Ключевые слова: PMC, SNP, психоактивные вещества, фенотип человек, виртуальный скрининг SNP, база данных SNP.

Работа выполнена при финансовой поддержке Российского фонда фундаментальных исследований (РФФИ) в рамках реализации проекта № 20-013-00145 "Механизмы комплексного влияния факторов окружающей среды на потребление психоактивных веществ населением локальных территорий Российской Федерации".