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Combined Influences of Genetic Factors and Attention Deficit Hyperactivity Disorder on the Development of Dependence on Synthetic Cannabinoids

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Objectives. To create a complex model of the individual risk of developing dependence on synthetic cannabinoids taking account of the combined influences of genetic predisposition and attention deficit hyperactivity disorder (ADHD). **Materials and methods.** A total of 146 male adolescents consuming synthetic cannabinoids and 136 healthy subjects (controls) were observed. Genetic studies assessed cases with the combination of these dependencies with ADHD. DNA was collected and six polymorphic loci of genes of the dopaminergic and serotoninergic systems were determined; results were analyzed using a series of special statistical methods. **Results and conclusions.** These data demonstrate the important role of the dopaminergic and serotoninergic systems in the pathogenesis of dependence on psychoactive substances and the significance of changes in the nucleotide sequences of the *DRD2*, *SLC6A3*, and *HTR2A* genes in the development of dependence on synthetic cannabinoids in males with ADHD.

Keywords: polymorphous gene loci, genes, psychoactive substance dependence, synthetic cannabinoids, attention deficit hyperactivity disorder.

Results from a number of studies have shown that attention deficit hyperactivity disorder (ADHD) is associated with an increased risk of developing dependence on psychoactive substances (PAS) and nicotine [1], and the prevalence of this syndrome is significantly greater among PAS addicts than in the general population [1]. A high level of heritability has been observed for ADHD (from 0.71 to 0.73), along with a concentration of cases of PAS dependence within families. Furthermore, the risk of developing PAS dependence is known to be greater among the relatives of probands with ADHD than among the relatives of healthy people [1].

Overlap between ADHD and PAS dependence may be mediated by a common genetic basis [2]. However, the nature of the pathogenetic mechanism underlying this overlap currently remains unclear. A whole set of neurobiological pathogenetic pathways are involved in both the development of ADHD and the development of dependence on PAS, including the dopaminergic and serotoninergic systems.

Changes in the functioning of the dopaminergic system of the brain play a significant role in in the development of PAS dependence. Use of these substances has been shown to lead to increases in extracellular dopamine, mainly in the ventral striatum [1]. Chronic PAS consumption leads to changes in neuroadaptation processes and a deficit in the dopaminergic reward system (for example, decreased accessibility of DRD2 receptors), which is regarded as a distinctive sign of addiction [1, 3]. In addition, the operation of the dopamine control inhibition mechanism (mainly mediated by the prefrontal cortex), which is also involved in the pathogenesis of PAS and nicotine dependence, is decreased [3]. First-line drugs for the treatment of ADHD are stimulators, which are believed to normalize the functioning of the dopaminergic frontostriatal connections [4]. These studies provide grounds

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for the view that changes in the operation of the genes of the dopaminergic system may mediate the risk of developing PAS and nicotine dependence in ADHD patients.

As noted above, the serotoninergic system is also involved in the pathogenesis of ADHD and PAS dependence [5, 6]. The serotoninergic raphe nuclei of the brain project to the striatum, modulating the dopamine reward system [5]. Alcohol and nicotine ingestion correlate with activation of the serotoninergic system. In fact, serotonin antagonists are effective in the treatment of alcoholism [1, 5]. Thus, genes influencing the functioning of the serotoninergic system may be involved in the overlap or comorbidity between PAS dependence and ADHD.

The genetic basis of complex diseases such as ADHD and PAS dependence is regarded as multifactorial, involving a multitude of polymorphic risk variants [7]. The polygenic risk factor can account for a larger proportion of the genetic contribution to the development of complex multifactorial diseases than association analysis for single polymorphic loci. Previous studies of polygenic risk for the development of maladaptive behavior [8] and food dependence [9] in ADHD have been reported.

Thus, attention should be paid to data evidencing the high prevalence and consumption of novel synthetic narcotics (NSN) in Russia as throughout the world [10]. Data from the European Monitoring Center for Drugs and Drug Addiction (EMCDDA, 2017) show that in 2014, most NSN exempt from control were synthetic cannabinoids (SCB) (60%), which have the slang name *spices* [11]. EMCDDA data (2017) show that in 2015, the SCB class included 25 novel substances among the 98 no previously identified or documented new psychotropic substances in the EC. The most frequent consumers of SCB were younger members of the population, predominantly adolescents [12].

SCB act on cannabinoid receptors, i.e., CB_1 and CB_2 receptors. Type 1 receptors are mostly on the presynaptic terminals of GABAergic and glutamatergic neurons and maintain homeostasis, preventing excessive or, conversely, insufficient activity via release of neurotransmitters by presynaptic regulation. Animal experiments have shown that activation of CB_1 receptors increases dopamine release from the nucleus accumbens [13]. Modulation of CB_1 receptors in turn leads to activation of the serotoninergic system via actions on 5-HT_{2A} or 5-HT_4 receptors [14].

Stimulatory actions on CB_1 receptors in the CNS lead to marked psychotropic effects (sedation, relaxation, impaired consciousness) [15]. Type 2 receptors are found in immune system cells, as well as in the brainstem and cerebellum. Stimulation of CB_2 receptors in immune system cells has been shown to produce immunomodulatory effects with anti-inflammatory actions. Studies have also shown that SCB block the broncholytic effect of acetylcholine in human lungs, leading to chronic damage [16].

The aim of the present work was to create a complex model for assessment of the individual risk of developing SCB dependence taking account of the combined effects of genetic predisposition and ADHD.

Materials and Methods. A total of 148 unrelated males with confirmed diagnoses of "Abuse of cannabinoids (synthetic cannabinoids)" (ICD-10, F12.1), i.e., SCB (spices) consumers, and 139 healthy men were included in the study. Mean age was 23.7 ± 0.8 years.

Blood samples from SCB addicts were obtained from the Republican Narcology Clinic, Ministry of Health of the Republic of Bashkortostan. Informed consent was obtained for use of patient's clinical material. The studies were approved by the Bioethics Committee of Bashkir State Medical University.

Inclusion criteria were a diagnosis of F12.1, "Abuse of cannabinoids (synthetic cannabinoids)," the absence of other dependencies (apart from caffeine and tobacco dependencies), age under 18 years, born in the Republic of Bashkortostan, absence of relatedness between subjects, male sex, and at least two follow-up observations during the six months before confirmation of SCB and/or their metabolic products in urine by gas chromatomass spectrometry (Strack, 2017).

Exclusion criteria were the absence of voluntary informed consent, confirmed concomitant psychopathology (schizophrenia, bipolar affective disorder, epilepsy), severe neurological symptomatology, marked cognitive impairments, severe somatic pathology, female sex, ongoing dependence on other PAS.

Analysis of the prevalence of ADHD in adolescents consuming SCB was used to form two groups. The first, study, group consisted of adolescents receiving hospital or out-patient treatment in the Republican Narcology Clinic No. 1 in 2013–2017 for SCB consumption. The mean age of the patients was 15.7 ± 0.7 years. The second, control, group consisted of adolescents of the same age as those of the study group. Clinical analysis then divided the study groups into ADHD(+) and ADHD(–) subgroups.

On day 5–6 of admission, all patients were interviewed in person by a psychiatrist to exclude or confirm ADHD. This took cognizance of the fact that in the ICD-10, ADHD is described in the section on disorders starting in childhood, with identification of two types of the condition: attention deficit without hyperactivity (F98.8) and attention deficit with hyperactivity (F90.0).

Venous blood DNA was prepared by standard phenol extraction [17].

Analysis of six polymorphic loci of genes in the dopaminergic and serotoninergic systems – rs1800497 of the *DRD2* gene, rs4646984 of *DRD4*, VNTR 40 b.p. and rs270272 of *SLC6A3*, rs6313 of *HTR2A*, and rs6296 of *HTR1B* – was conducted using the polymerase chain reaction for DNA synthesis and RFLP analysis followed by electrophoresis in 7–8% polyacrylamide gels [18–22].

The role of the factors of interest in forming the predisposition to develop SCB dependence was assessed using

TABLE 1. Assessment of Coefficients of Unifactorial Logistical Regression Equations in SCB Addicts

Measure	*B*	*p*	OR (exp*B*)	95% CI
*DRD2*_rs1800497		0.00		
A1/A1	0.68	0.00	1.97	1.33–2.91
A1/A2	–0.48	0.00	0.62	0.45–0.86
A2/A2	–0.20	0.25	0.82	0.59–1.14
Constant	0.18	0.16	1.19	
*DRD4*_rs4646984		0.09		
L/L	0.47	0.03	1.60	1.05–2.43
L/S	0.22	0.35	1.24	0.78–1.97
S/S	–0.69	0.06	0.50	0.25–1.02
Constant	–0.27	0.17	0.76	
Presence of *SLC6A3*9/9* genotype	0.69	0.007	1.987	1.21–3.27
Constant	–0.17	0.244	0.843	
*SLC6A3*_rs27072		0.19		
C/C	0.02	0.93	1.02	0.68–1.53
C/T	0.35	0.07	1.42	0.97–2.08
T/T	–0.37	0.24	0.69	0.38–1.27
Constant	–0.12	0.49	0.89	
*HTR2A*_rs6313		0.03		
A/A	0.22	0.40	1.24	0.75–2.04
A/G	–0.42	0.02	0.66	0.46–0.93
G/G	0.21	0.26	1.23	0.86–1.76
Constant	0.16	0.27	1.18	
*HTR1B*_rs6296		0.55		
C/C	–0.21	0.27	0.81	0.56–1.18
C/G	–0.03	0.87	0.97	0.68–1.39
G/G	0.24	0.38	1.27	0.74–2.17
Constant	0.14	0.38	1.15	
Presence of ADHD	2.54	0.00	12.73	5.26–30.82
Constant	–0.35	0.01	0.71	

Here and Table 2: *B* is the coefficient of the logistical regression equation; *p* is the level of statistical significance; OR (exp*B*) is the odds ratio.

a statistical method based on construction of logistical regression models with stepwise exclusion of the least significant factors. The suitability of the resulting mathematical models was evaluated in terms of the area under the ROC curve (AUC) and their 95% confidence intervals (CI) [23]. Analyses were run in SPSS 22.0.

Results. Logistical regression analysis results for all polymorphic gene variants are shown in Table 1. The *rs21800497*A1/A1* genotype of the *DRD2* gene increased the risk of developing SCB dependence in individuals with ADHD (OR = 1.97), while the *rs6313*A/G* genotype of the *HTR2A* gene, conversely, produced a decrease (OR = 0.66). The remaining polymorphic markers studied showed no statistically significant differences (see Table 1).

A complex genetic model for the risk of developing SCB dependence was constructed by logistical regression.

TABLE 2. Coefficients of Logistical Regression Equation for Four Independent Genetic Factors for the Development of Dependence on SCB Components, i.e., Components of the Complex Genetic Model

Marker	*B*	*p*	exp*B*	95% CI for exp*B*	
				lower	upper
ADHD (1) No	–1.343	0.000	0.261	0.164	0.415
ADHD (1) Yes	1.343	0.000	3.830	2.407	6.093
*DRD2*_rs1800497		0.000			
A1/A1	0.758	0.001	2.135	1.389	3.281
A1/A2	–0.705	0.000	0.494	0.337	0.725
A2/A2	–0.054	0.081	0.776	0.948	0.655
*SLC6A3*_V40_9/9	0.787	0.007	2.198	1.246	3.877
*HTR2A*_rs6313		0.106			
A/A	0.257	0.366	1.292	0.741	2.254
A/G	–0.402	0.044	0.669	0.452	0.989
G/G	0.146	0.481	1.157	0.772	1.734
Constant	1.330				

TABLE 3. ROC Analysis Data for Separate Genetic Risk Factors and the Complex Genetic Marker for the Risk of Developing SCB Dependence

Measure	AUC	Standard error	Asymptomatic value b	Asymptomatic 95% CI	
				lower limit	upper limit
ADHD	0.661	0.032	0.000	0.598	0.724
ADHD and markers	0.781	0.027	0.000	0.728	0.835
Markers	0.676	0.032	0.000	0.614	0.738

pAUC – *p* calculated using the DeLong method. Test results for variable or variables: predicted probability of at least one relationship between the positive current status group and the negative current status group. The statistic may be biased. a) Nonparametric assumption; b) null hypothesis: true area = 0.5.

The analysis included consideration of the genetic markers described in our previous studies: rs1800497 of the *DRD2* gene, rs4646984 of *DRD4*, VNTR40 b.p. and rs27072 of *SLA6A3*, rs6313 of *HTR2A*, and rs6296 of *HTR1B* and ADHD status [11].

Table 2 shows the coefficients of the regression equation for its variables – three genetic markers and ADHD status, included in the complex model. These coefficients were statistically significant ($p < 0.05$) both for the polymorphic markers rs1800497 of the *DRD2* gene, VNTR 40 b.p. of *SLC6A3*, and rs6313 of *HTR2A*, and for ADHD status (see Table 2).

The prognostic significance of the resulting complex genetic marker and its component genetic risk factors taken separately were evaluated by ROC analysis (Table 3). It follows from Table 3 that separate consideration of the genetic risk factors in the study cohort were weak markers for the risk of developing SCB dependence (AUC 0.661 and 0.676). At the same time, the complex model (genetic risk factors and ADHD status) demonstrated greater prognostic significance in the cohort studied here (AUC = 0.781).

Thus, the complex genetic marker is stable and has undoubted advantages over other genetic markers for appropriate evaluation of the influences of genetic factors on the probability of development of SCB dependence in individuals with ADHD.

Results from the logistical regression analysis used for construction of ROC curves were employed for analysis of the quality of the resulting models. In version 1, the only predictor was ADHD status; in version 2, the polymorphic markers from our studies were used, while version 3 used ADHD status and polymorphic markers (see Fig. 1). It follows from these results that that simultaneous use of polymorphic markers rs1800497 of the *DRD2* gene, VNTR 40 b.p. of *SLC6A3*, and rs6313 of *HTR2A* as predictors of ADHD status gives a better predictive model for assessment of the predisposition to developing SCB dependence. Analysis of the coefficients of the regression equation and ROC curves (see Fig. 1) shows that the complex marker obtained here had greater prognostic effectiveness (AUC = 0.781) than analysis of the factors included in the model taken separately.

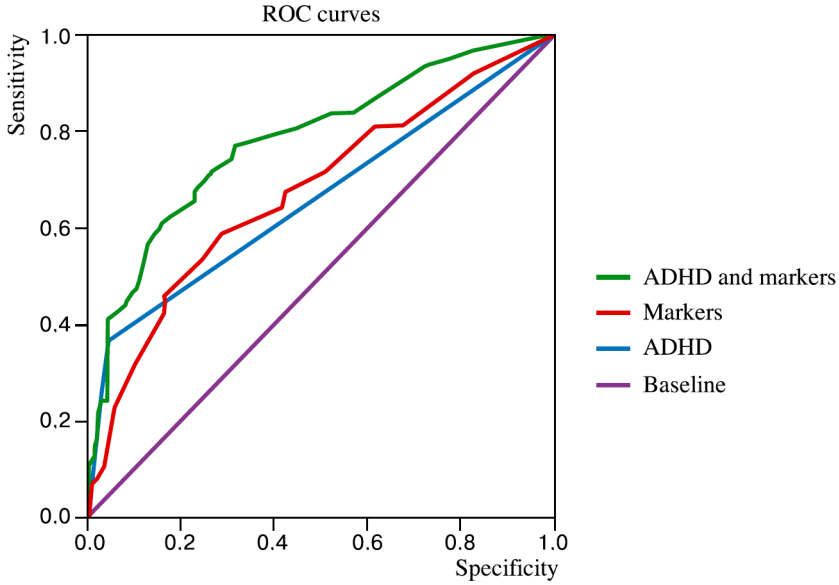

Fig. 1. Area under the curve (AUC) for individual genetic risk factors and the complex genetic marker for the risk of developing SCB dependence.

Discussion. This paper describes an attempt to use logistical regression to create a complex model for assessment of the individual risk of developing SCB dependence considering the contributions of the dependence predictors identified in our previous studies [11] and the presence or absence of ADHD. The first step in this process consisted of forming a complex genetic marker including three genetic risk factors: rs1800497 of the *DRD2* gene, VNTR 40 b.p. of *SLC6A3*, and rs6313 of *HTR2A*, for which we have previously described associations with SCB dependence (see Table 1) [11]; a marker for the presence or absence of ADHD was then added to obtain a complex marker for this complex genetic marker.

As this model includes a restricted number of genetic and traditional risk factors, we regard it as a prototype. Nonetheless, the complex marker obtained here has high prognostic effectiveness (AUC $\approx$ 0.781).

Our data fit the notion that genetic predisposition is an important risk factor for the development of SCB dependence in individuals with ADHD.

In creating a complex marker, we studied not only genetic factors, but also the influence of an important risk factor – ADHD. At this stage of the study, we did not consider other risk factors, taking account of the fact that creation of a complex marker might be hindered by possible interactions between genetic and other factors.

The results of the present study confirm results from studies of the involvement of the serotoninergic system in the development of PAS dependence [5], demonstrating the role of serotonin at the early stages of formation of PAS dependence in individuals with ADHD (see Table 2). Previous studies demonstrated high heritability of patients' age at onset of addiction [24]. Serotonin and dopamine have roles in the development of impulsive behavior [25], which may in turn be a symptom of both ADHD and PAS dependence. However, impulsivity itself differs in terms of clinical signs, while dopamine and serotonin do not have identical correlations with different types of impulsivity [25]. The current study also confirms the involvement of the dopaminergic system in the mechanisms of development of PAS dependence. We were able to show that the polymorphous loci of the rs1800497 of the *DRD2* gene and VNTR 40 b.p. of *SLC6A3* are predictors of the development of SCB in individuals with ADHD (see Table 2).

Animal experiments have shown that mice with knockout of the *HTR1B* gene display hyperactivity and aggressivity [27, 28], increased exploratory activity [27], impaired attention, and other symptoms typical of ADHD in humans [29, 30]. Genetic investigations of the polymorphic locus rs6296 of the *HTR1B* gene were contradictory. Thus, results from a number of studies have demonstrated an association between the *rs6296*G* allele and the development of ADHD [31–35] and this has been confirmed by a meta-analysis of nine association studies [36]. However, later work established an association between the *rs6296*C* allele of the *HTR1B* gene with ADHD in Indians [37] and Chinese [38], which was not confirmed among the inhabitants of Colombia [39] and was consistent with the results of the present study (see Table 2).

The polymorphic locus rs6313 of the *HTR2A* gene, synonymous to the T102C substitution, is in complete linkage disequilibrium with the polymorphic variant rs6311 of the *HTR2A* gene, modulating the activity of the gene [40].studies have shown that the *rs6313*T* allele of the *HTR2A* gene has greater affinity for the receptor and that the *rs6313*T/T* genotype correlates with a low serotonin level, which is very

strongly linked with pulse inhibition. Studies reported by Li and Elia showed a predominance of the *rs6313*T* allele in Indians [31, 41], which is consistent with results from this study (see Table 2). Conversely, other investigators have established an association between the *rs6313*C* allele with ADHD in Europeans [42]. Similar noncorrespondences are linked with different allele frequencies in different ethnic groups and with the clinical heterogeneity of ADHD. Future studies need to have larger cohorts and must address other polymorphic variants of the genes studied.

A meta-analysis [36] established significant associations with polymorphic variants of the *SLC6A3*, *DRD4*, and *HTR1B* genes. Despite contradictory results, an ADHD genetic database [43] indicates that specific alleles of polymorphic variants of the *DRD4* gene have been identified in association with ADHD in more than 70% of cases. At the same time, the significant association percentage for the polymorphic marker of the *SLC6A3* gene was rather lower, at about 60%.

A number of studies have addressed the dopamine transporter gene *SLC6A3*, especially the VNTR 40 b.p. polymorphic variant in the 3' region of the *SLC6A3* gene [44]. The *V40*10* allele in adolescents and the *V40*9* allele in adult individuals are associated with increases in dopamine *SLC6A3* transporter activity measured by positron emission tomography [44], which is consistent with the results of the present study (see Table 2).

The results obtained here demonstrate that the *DRD2*, *SLC6A2*, and *HTR2A* genes of the serotoninergic and dopaminergic systems are predictors for the development of SCB dependence in individuals with ADHD. In addition, ADHD has been shown to be a good predictor for the development of SCB dependence.

Thus, our study presents the concept that there are common genetic bases for these highly comorbid disorders.

The complex marker proposed here, which has stable prognostic effectiveness, can be used as the basis for creating a prognostic test for assessment of individual risk of developing SCB dependence. However, these results need to be reproduced in other populations, with particular interest in prospective studies.

The authors have no conflicts of interests.

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