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HUMAN GENETICS

The Role of Intergenic Interactions of Neurotrophic and Neurotransmitter System Genes in the Development of Susceptibility to Paranoid Schizophrenia

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Abstract—The purpose of this study was to analyze the gene-gene interactions of 70 polymorphic variants of six genes of the neurotrophin and neurexin system (*BDNF*, *NTRK2*, *NTRK3*, *NGF*, *NXPH1*, *NRXN1*) and nine genes of the neurotransmitter system (*DRD2*, *DRD3*, *DRD4*, *COMT*, *GRM3*, *GRIK2*, *GRIA2*, *GRIN2B*, *RGS2*) in determining the risk of developing paranoid schizophrenia in ethnic groups of Russians and Tatars.

Keywords: genetics, schizophrenia, genes of the system of neurotrophins and neurexins, genes of the neurotransmitter system, intergenic interactions

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INTRODUCTION

Since the hereditary predisposition to schizophrenia, as a multifactorial disease, is based on a specific combination of alleles of many genes that affect the development of the disease or modify its clinical manifestations, and analysis of the association of individual polymorphic gene variants cannot provide a complete picture of the mechanisms of paranoid schizophrenia formation (PS), when predicting the risk of developing PS, it is necessary to take into account intergenic interactions. Thus, when analyzing the genetic component of schizophrenia susceptibility, we obtained several convincing examples of the importance of genetic interactions in the development of this disease in Chinese people [1, 2], Indian people [3], and English people [4].

In general, genetic studies have shown the complexity of the genetic architecture of schizophrenia, as well as its polygenic nature. One hypothesis is that one or more pathogenesis pathways combine many empirical data from schizophrenia. However, the mechanisms by which these single nucleotide variants increase the risk of schizophrenia are still unclear. The biological role of single nucleotide polymorphic (SNP) variants and how they interact with other genes and environmental factors is not yet clear [5]. It was revealed that many functionally interconnected genes are involved in the etiopathogenesis of schizophrenia, including genes of dopaminergic, glutamatergic, and serotonergic neurotransmission, the family of neurotrophins and neurexins, and signal transduction [6–11].

The most famous approach for modeling intergenic interactions is the MDR bioinformatic method for studying multilocus genotypes. In the MDR program, multilocus genotypes are summarized into groups of increased and reduced risk of the disease, which reduces the dimensionality of the number of parameters considered. By repeatedly cross-recalculating the input primary data, the program selects the optimal model of intergenic interactions, which allows predicting the presence or absence of a predisposition to a particular disease with the highest accuracy and with the least error.

The purpose of this study is analysis of intergenic interactions of 44 polymorphic variants of six genes of the system of neurotrophins and neurexins (*BDNF*, *NTRK2*, *NTRK3*, *NGF*, *NXPH1*, *NRXN1*) and 26 SNPs of nine genes of the neurotransmitter system (*DRD2*, *DRD3*, *DRD4*, *COMT*, *GRM3*, *GRIK2*, *GRIA2*, *GRIN2B*, *RGS2*) in determining the risk of developing paranoid schizophrenia in ethnic groups of Russians and Tatars.

MATERIALS AND METHODS

Representatives of the two most common populations of Bashkortostan, Russians and Tatars, were included in the studied samples, since it is known that the prevalence of functionally significant genetic variations, the structure of haplotypes and linkage disequilibrium, and their association with a particular

disease depends on the ethnic history of the population [12, 13].

The main study group included 257 unrelated individuals (137 males, 120 females) with a diagnosis of paranoid schizophrenia with a continuous and episodic type of disease. The examined were patients of the Republican Clinical Psychiatric Hospital No. 1 of the Ministry of Health of the Republic of Bashkortostan. The diagnosis was made in accordance with the international classification of diseases of the tenth revision (ICD-10). The average age of patients was 24.9 ± 8.9 years. The mean age at onset of the disease was 22.4 ± 7.3 years. For each patient, through an individual survey and analysis of the medical history, a specially designed questionnaire was filled out, in which passport data of patients, complaints, clinical and anamnestic data, and all ongoing general clinical and special research methods were entered. The composition of the general sample of patients with paranoid schizophrenia by ethnicity is as follows: Russians—108, Tatars—149.

As a control, 349 individuals (174 Russians, 175 Tatars) of the same age group who were not registered with a psychiatrist and narcologist and had a negative hereditary predisposition to mental illnesses were examined. The average age of healthy donors was 32.4 ± 12.4 years.

All participants of the study or their legal representatives gave informed consent to conduct molecular genetic studies. This study was approved by the local bioethics committee of the Institute of Biochemistry and Genetics.

DNA was isolated from peripheral blood using the standard phenol-chloroform extraction method [14]. Analysis of polymorphic loci *DRD2* (rs1800497, rs6275), *DRD3* (rs6280), *DRD4* (–616C>G, 120-bp VNTR), *COMT* (rs4680, rs4818), *GRIN2B* (rs34315573, rs1805502, rs7301328, rs1805482, rs1805247, rs1805476), *RGS2* (rs2746073, rs2746072, rs3767488, rs2746071, rs4606), *GRIK2* (rs2235076, rs2227283, rs995640, rs2227281), and *GRM3* (rs274622, rs187993, rs6465084) was performed using the polymerase chain reaction (PCR) method of DNA synthesis and RFLP analysis followed by electrophoresis in 7–8% polyacrylamide gel [6–8, 11].

Genotyping of polymorphic variants of rs6536221, rs4441804, and rs4302506 gene *GRIA2* was performed using TaqMan® SNP Genotyping Assays C-29062108_10 and TaqMan® Genotyping Master Mix (Applied Biosystems) according to the protocol of the manufacturer [8].

Genotyping of 44 polymorphic loci of genes of the neurotrophic factor system and subsequent recognition of genotypes was performed on the SNPlex™ platform (Applied Biosystems) and using the program GeneMapper 4.0 (Applied Biosystems) according to the protocol of the manufacturer [9].

When analyzing intergenic interactions, the type of interaction between loci (synergy, additivity, or synonymy) was determined using the programs MDR (Multifactor Dimensionality Reduction) [15, 16]. In addition, the amendment FDR-BH (False Discovery Rate Bengamini-Hochberg) for the number of multiple comparisons [17] was introduced.

RESULTS

In patients with paranoid schizophrenia and in the control group, the intergenic interactions of the studied polymorphic loci of the candidate genes for the development of this disease were evaluated in determining the risk of developing PS. To sample the models, we used the exhaustive search algorithm, which evaluated all possible combinations of genotypes with respect to the risk of developing PS, and the forced search algorithm, in which polymorphic gene loci were selected manually to study the genotype combinations. For each model of intergenic interactions, the frequencies of genotypes of interacting genes in the samples of patients and healthy individuals were compared.

A study of gene-gene interactions in individuals of different ethnicities showed that, in Russians, two-locus models are the optimal models predisposing to the development of paranoid schizophrenia: *DRD2* × *COMT* and *RGS2* × *GRIN2B* (Table 1).

In the group of individuals with paranoid schizophrenia and control in Russians, ethnicity is statistically significant ($p = 0.0107$) and the model determined a combination of two DNA loci, genes *DRD2* (rs1800497) and *COMT* (rs4680), whose interaction underlies the predisposition to the development of paranoid schizophrenia. The tested balanced accuracy (*Bal. Acc.*) of this model was 0.74, the sensitivity (*Se*) was 0.70, the specificity (*Sp*) was 0.77, and the reproducibility of the result (*CV* Consistency) was 7/10 (Fig. 1a, Table 1).

Three different combinations of genotypes were assigned to combinations of the increased risk of developing the disease (highlighted with a dark gray background), of which the most significant was *rs1800497*A2/A2* and *rs4680*A/A* ($p = 0.012$, $OR = 3.25$, CI95% 1.36–7.79). Three different combinations of genotypes were assigned to combinations of a reduced risk of developing the disease (highlighted by a light gray background); however, none of them reached statistical significance (Fig. 1a).

The results of the study are partially consistent with the data obtained as a result of analysis of the association at individual gene loci *DRD2* showing that the genotype *rs1800497*A2/A2* increases the risk of developing PS in Russians (Table 2). Single-locus analysis did not establish an SNP rs4680 gene *COMT* association with the risk of developing PS in any of the ethnic groups, while the analysis of intergenic interactions revealed a combination of SNP rs4680 gene *COMT* and rs1800497 gene *DRD2*, which may be explained by

Table 1. Key intergenic interactions that determine the predisposition to the development of paranoid schizophrenia in Russians and Tatars

Optimal model for intergenic interaction	Balanced accuracy (*Bal. Acc.*)	Sensitivity (*Se*)	Specificity (*Sp*)	Precision (*CV* Consistency)	*p*
Russians					
DRD2 × *COMT*	0.74	0.70	0.77	7/10	1.0E–03
RGS2 × *GRIN2B*	0.64	0.59	0.68	10/10	0.012
Tatars					
GRM3 × *DRD2*	0.71	0.62	0.81	8/10	1.0E–03
BDNF × *NTRK2*	0.56	0.60	0.51	10/10	1.57E–03
NXPH1 × *NTRK3*	0.62	0.63	0.61	10/10	1.01E–04
NTRK3 × *BDNF*	0.58	0.47	0.70	10/10	0.002

p, level of statistical significance.

the epistatic action of genes, which plays an important role in the determination of biological traits [18]. No published data describing this model of gene interaction obtained by us with a risk of schizophrenia were found. Some studies have shown that the model of gene-gene interaction of *COMT* and *DRD2* is associated with creativity (rs174675, rs4818 gene *COMT*; rs1076560, rs4648317 gene *DRD2*) [19] and anorexia nervosa (rs4633 gene *COMT* and rs1800497 *DRD2*) [20] among the Chinese. This gene interaction, leading to an increased risk of PS development, can be explained, firstly, by an increase in dopamine activity associated with the allele *rs1800497*A2* in the gene *DRD2* in which there is an excess of dopamine, and secondly, the enzyme COMT, containing methionine (allele *rs4680*A* in the gene *COMT*) in a homozygous state, has fourfold less activity, leading to a slowdown in dopamine degradation in the prefrontal cortex [21].

Thus, these processes can cause an excess of dopamine in patients with paranoid schizophrenia. Our data are consistent with the hypothesis of the activation of the dopaminergic system in schizophrenia.

In the group of individuals with PS and the control among Russians, ethnicity is statistically significant ($p = 0.0107$) and the model determined a combination

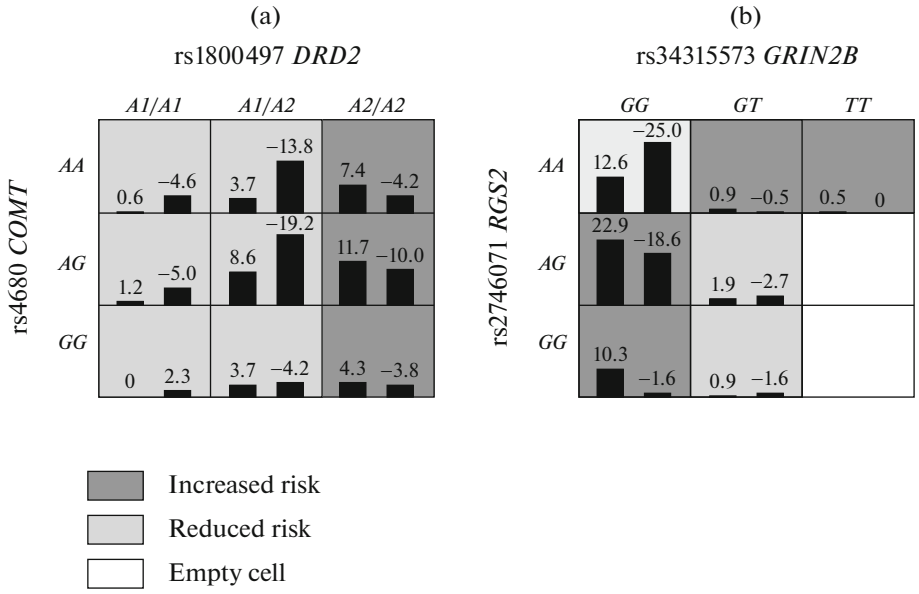

Fig. 1. (a) Combinations of genotypes of polymorphic loci of genes *DRD2* (rs1800497) and *COMT* (rs4680) associated with an increased and decreased risk of developing PS among Russians; (b) combinations of genotypes of polymorphic loci of genes *RGS2* (rs2746071) and *GRIN2B* (rs34315573) associated with an increased and decreased risk of developing PS in Russian.

Table 2. Combinations of genotypes of increased and reduced risk of paranoid schizophrenia

Combination of genes	Combination of SNPs and genotypes	*p*	p_{fdr}	*OR*	CI95%
Russians					
DRD2 × *COMT*	*rs1800497*A2/A2* × *rs4680*A/A*	0.012	0.016	3.25	1.36–7.79
	*rs1800497*A2/A2* × *rs4680*A/G*	0.026	0.026	2.27	1.15–4.46
RGS2 × *GRIN2B*	*rs2746071*G/G* × *rs34315573*G/G*	4E-04	0.0016	7.85	2.26–27.18
	*rs2746071*A/A* × *rs34315573*G/G*	5E-04	0.001	0.33	0.18–0.61
Tatars					
NXPH1 × *NTRK3*	*rs10272916*C/C* × *rs11631508*A/A*	0.0063	0.014	3.52	1.39–9.05
	*rs10272916*C/C* × *rs11631508*G/G*	0.0278	0.038	0.0005	0.66–0.81
NTRK3 × *BDNF*	*rs3825884*C/T* × *rs7124442*T/T*	0.0423	0.042	1.81	1.02–3.21
	*rs3825884*C/T* × *rs7124442*C/T*	0.0416	0.048	0.54	0.30–0.98
GRM3 × *DRD2*	*rs6465084*A/A* × *rs6275*C/T*	0.001	0.007	3.16	1.62–6.16
	*rs6465084*A/A* × *rs6275*T/T*	0.005	0.0175	3.11	1.43–6.76
	*rs6465084*G/G* × *rs6275*T/C*	0.023	0.04	0.33	0.13–0.82

p, level of statistical significance; p_{fdr}, level of statistical significance adjusted for multiple FDR comparisons; *OR*, odds ratio.

of two DNA loci, *RGS2* (rs2746071) and *GRIN2B* (rs34315573), the interaction of which underlies the predisposition to the development of paranoid schizophrenia. The tested balanced accuracy (*Bal. Acc.*) of this model was 0.64, the sensitivity (*Se*) was 0.69, the specificity (*Sp*) was 0.58, and the reproducibility of the result (*CV* Consistency) was 10/10 (Fig. 1b, Table 1).

To combinations of an increased risk of developing the disease (Fig. 1b, highlighted by a dark gray background), four different combinations of genotypes were assigned, of which the most significant was *rs2746071*G/G* and *rs34315573*G/G* ($p = 0.0004$, $OR = 7.85$, CI95% 2.26–27.18). Three different combinations of genotypes were assigned to combinations of a reduced risk of developing the disease, of which the most significant was *rs2746071*A/A* and *rs34315573*G/G* ($p = 0.0005$, $OR = 0.33$, CI95% 0.18–0.61) (Table 2).

The results of this study are partially consistent with the data obtained as a result of analysis of the association at individual loci of gene *RGS2* and analysis of haplotypes showing that the genotype *rs2746071*A/A* lowers the risk of developing PS in Russians and Tatars [7]. Single-locus analysis did not establish the association of SNP rs34315573 gene *GRIN2B* with the risk of developing PS in any of the ethnic groups, while the analysis of intergenic interactions revealed a combination of single-nucleotide polymorphic variants (SNPs) of the rs34315573 gene *GRIN2B* and rs2746071 gene *RGS2*, which is possibly explained by the epistatic effect of genes. No published data describing the model of gene interaction that we have obtained with the risk of developing schizophrenia has been found. This gene interaction, leading to an increased risk of developing PS, can be explained by the fact that *RGS2* accelerates G-protein deactivation to reduce the response of a neuronal receptor conjugated to the GPCR G protein with neurotransmitters [22], including glutamate. Presumably, this interaction can be associated with the pathogenesis of schizophrenia and other mental illnesses, which is also consistent with the hypofunction of the glutamatergic system in patients with PS [3].

When analyzing intergenic interactions in individuals of Tatar ethnicity, four two-locus models were determined that determine the development of PS—*BDNF* × *NTRK2*, *NXPH1* × *NTRK3*, *BDNF* × *NTRK3*, *GRM3* × *DRD2* (Table 1). In the group of people with PS and the control among Tatars (by ethnicity), a combination of two DNA loci was determined by the statistically significant ($p = 0.0010$) model: *GRM3* (rs6465084) and *DRD2* (rs6275), the interaction of which underlies the predisposition to the development of paranoid schizophrenia. The tested balanced accuracy (*Bal. Acc.*) of this model was 0.71, the sensitivity (*Se*) was 0.62, the specificity (*Sp*) was 0.81, and the reproducibility of the result (*CV* Consistency) was 8/10 (Fig. 2a, Table 1).

Three different combinations of genotypes were assigned to combinations of an increased risk of developing the disease, of which the most significant was

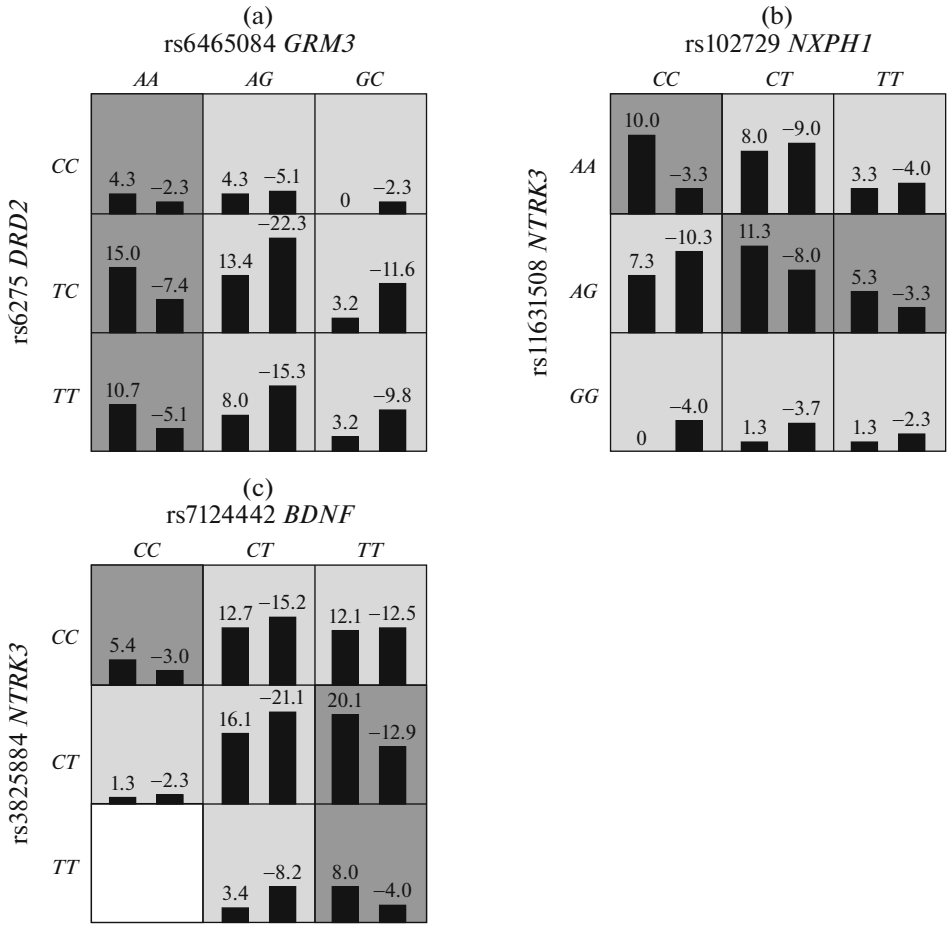

Fig. 2. (a) Combinations of genotypes of polymorphic loci of genes *GRM3* (rs6465084) and *DRD2* (rs6275) associated with an increased and decreased risk of developing PS among Tatars; (b) combinations of genotypes of polymorphic loci of genes *NXPH1* (rs10272916) and *NTRK3* (rs11631508) associated with an increased and decreased risk of developing PS in Tatars; (c) combinations of genotypes of polymorphic loci of genes *NTRK3* (rs3825884) and *BDNF* (rs7124442) associated with an increased and decreased risk of developing PS in Tatars.

*rs6465084*A/A* × *rs6275*T/T* ($p = 0.001$, $OR = 3.16$, CI95% 1.62–6.16); *rs6465084*A/A* and *rs6275*C/T* ($p = 0.005$, $OR = 3.11$, CI95% 1.43–6.76). Six different combinations of genotypes were assigned to combinations of a reduced risk of developing the disease, of which the most significant was *rs6465084*G/G* × *rs6275*T/C* ($p = 0.023$, $OR = 0.33$, CI95% 0.13–0.82) (Table 2).

The results of the study are partially consistent with the data obtained as a result of analysis of the association at individual gene loci *GRM3* showing that the genotype *rs6465084*A/A* increases and *rs6465084*G/G* lowers the risk of developing PS in Tatars [11].

However, in a single-locus analysis, no association of SNPs of the rs6275 gene *DRD2* with the risk of developing PS was found in any of the ethnic groups, while the analysis of intergenic interactions revealed the interaction of the rs6275 gene *DRD2* and rs6465084 gene *GRM3*. This is possibly explained by the epistatic action of genes, which plays an important role in the determination of biological traits [18]. No literature data describing this model of gene-interaction obtained by us were found. However, this interaction can be explained by the existence of the interaction of the dopaminergic and glutamatergic systems and its role in the pathogenesis of schizophrenia, in which the disruption in the work of these two neurotransmitter systems reinforces each other [21].

In the group of people with paranoid schizophrenia and the control of Tatars, ethnicity is statistically significant ($p = 0.00157$) and the model determined a combination of two DNA loci, *BDNF* (rs1491850) and *NTRK2* (rs1899640), the interaction of which underlies the predisposition to the development of paranoid schizophrenia. The tested balanced accuracy (*Bal. Acc.*) of this model was 0.56, the sensitivity (*Se*) was 0.60, the specificity (*Sp*) was 0.51, the reproducibility of the result (*CV* Consistency) was 10/10 (Table 1). However, since the specificity of this model was 51%, it was excluded from further analysis.

In the study of gene-gene interactions of the studied polymorphic loci using the MDR program, a two-locus model of the interaction of DNA loci was determined, *NXPH1* (rs10272916) and *NTRK3* (rs11631508), leading to the development of PS in the group of Tatar ethnicity (Fig. 2b, Table 1). The tested balanced accuracy (*Bal. Acc.*) of this model was 0.62, the sensitivity (*Se*) was 0.63, the specificity (*Sp*) was 0.61, and the repeatability of the result (*CV* Consistency) was 10/10, $p = 0.00101$ (Fig. 2b, Table 1).

Four different combinations of genotypes were assigned to combinations of an increased risk of developing the disease, of which the most significant was *rs10272916*C/C* and *rs11631508*A/A* ($p = 0.0063$, $OR = 3.52$, CI95% 1.39–9.05). Four different combinations of genotypes were assigned to combinations of a reduced risk of developing the disease, of which the most significant was *rs10272916*C/C* and *rs11631508*G/G* ($p = 0.0278$, $OR = 0.0005$, CI95% 0.66–0.81) (Table 2).

A statistically significant two-locus model of gene interaction was also found in a group of individuals with PS and control of Tatar ethnicity: *NTRK3* (rs3825884) and *BDNF* (rs7124442) (Fig. 2c, Table 1). The balanced accuracy (*Bal. Acc.*) of this model was 0.58, the sensitivity (*Se*) was 0.47, the specificity (*Sp*) was 0.70, and the reproducibility of the result (*CV* Consistency) was 10/10, $p = 0.001673$ (Fig. 2c, Table 1). Three combinations of high-risk genotypes were identified, of which the most significant was *rs3825884*C/T* and *rs7124442*T/T* ($p = 0.04$, $OR = 1.81$, CI95% 1.02–3.21), and five combinations of low-risk genotypes were identified, of which the most significant was *rs3825884*C/T* and *rs7124442*C/T* ($p = 0.0447$, $OR = 0.5$, CI95% 0.25–0.98) (Table 2).

DISCUSSION

As a result of this study, the interaction of SNP genes *NTRK3* (rs11631508) and *NXPH1* (rs10272916) was found, increasing and decreasing the risk of PS in Tatars, which is partially consistent with the data of a unilocus analysis of the association, which showed the association of SNPs rs1946698, rs7170062, and rs11631508 gene *NTRK3* and rs7801099 gene *NXPH1* in Russians with a risk of developing PS [9]. No published data describing this model of gene interaction obtained by us was found. However, it is known that the gene *NTRK3* is involved in the development of oligodendrocytes and myelination of nerve fibers of the brain [23]. There are isolated data that indicate the role of neuroxyphilins in the mechanism of sensory processing of information and coordination of movements [24] and involvement of gene *NXPH1* in the development of autism spectrum diseases in Europeans [25]. On the basis of data on an increase in the expression level of these genes in the hippocampus, it can be assumed that they are involved in the pathogenesis of schizophrenia.

As a result of this study, the interaction of SNP genes *NTRK3* (rs3825884) and *BDNF* (rs7124442) was found, increasing and decreasing the risk of PS in Tatars, which is partially consistent with the data of a unilocus analysis of the association, which showed the association of SNPs rs1946698, rs7170062, and rs11631508 gene *NTRK3* in Russians. However, we did not identify any association of individual SNPs and haplotypes of gene *BDNF* with a risk of developing PS in Russians and Tatars [9]. No published data describing this model of gene-interaction obtained by us were found. However, these results can be interpreted on the basis of the important role of neurotrophic factors in the development of the brain and synaptic plasticity.

The results of the analysis of modeling of intergenic interactions are partially consistent with the results of a study of Z. Lin et al. also showing the interaction of genes *BDNF* and *NTRK2*, increasing the risk of developing paranoid schizophrenia in the Chinese. However, in a study of Z. Lin et al., a model was established with the participation of SNPs alone: *NTRK2* (rs1387923, rs2769605) × *BDNF* (rs6265) [26], and in this study with other SNPs. Previous results also demonstrated interaction of genes *BDNF* and *NTRK2* among Europeans [27], Africans [28], and Chinese [29, 30]. In this study, no association with the risk of developing PS at individual polymorphic loci of the rs1491850 gene *BDNF* and rs1899640 gene *NTRK2* or in the analysis of haplotypes was found either in the ethnic group of Russians or among Tatars. Therefore, this is possibly associated with the sample size, and this model *BDNF* × *NTRK2* was excluded from further analysis, since the specificity of this model was 51%. It should be noted that schizophrenia is a complex disease. Certain genetic variants can have only insignificant, difficult to detect, effects on its pathogenesis. Perhaps in the development of schizophrenia, BDNF and its receptor NTRK2 may act synergistically, but so far we do not know how. In addition, the NTRK2 receptor is known to have high affinity for BDNF and the BDNF/NTRK2 signaling pathway plays a key role in the pathogenesis of schizophrenia [31].

On the basis of the obtained data on the models of intergenic interactions, as well as the results of the previous study, a cluster analysis was performed using the MDR method, showing the nature of the interaction between the polymorphic loci of the genes of neurotrophins, neurexins, and neurotransmitter systems in Russians and Tatars (Figs. 1, 2).

Polymorphic loci of gene *NTRK3* and gene *NXPH1*, as well as SNPs of gene *NRXN1* and gene *NXPH1* act synergistically; interactions of SNPs of other genes exhibit a synonymous effect (Figs. 3–5).

CONCLUSIONS

Thus, the analysis of intergenic interactions made it possible to establish DNA loci of the studied genes

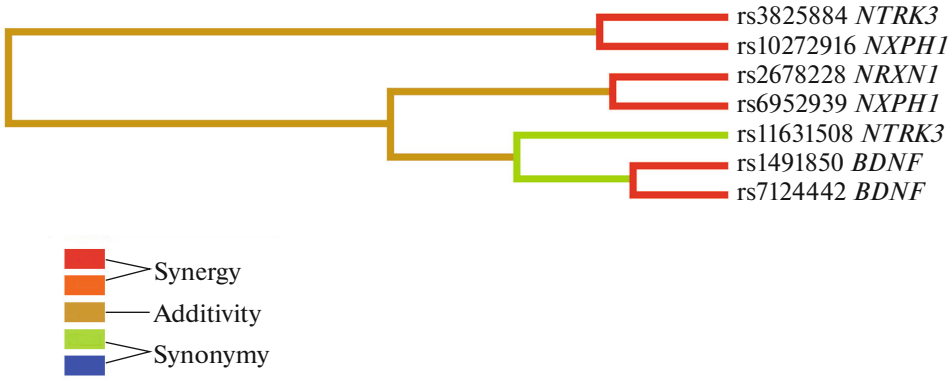

Fig. 3. Intergenic interactions of polymorphic loci of neurotrophin genes involved in the formation of a predisposition to PS in Tatars.

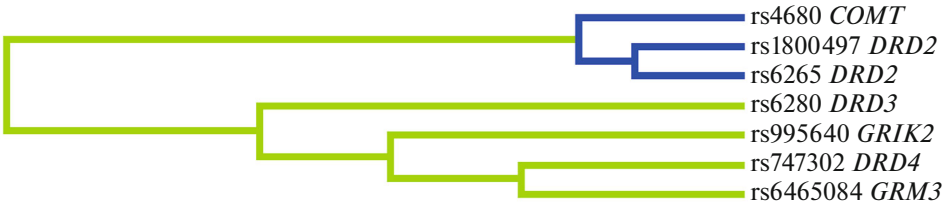

Fig. 4. Intergenic interactions of polymorphic loci of genes of neurotransmitter systems involved in the formation of a predisposition to PS in Tatars.

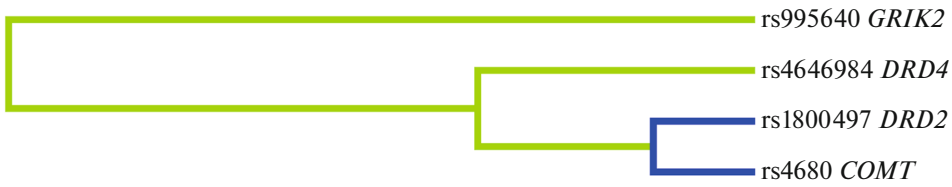

Fig. 5. Intergenic interactions of polymorphic loci of genes of neurotransmitter systems involved in the formation of a predisposition to PS in Russians.

that interact during the formation of a predisposition to paranoid schizophrenia in Russians and Tatars. In both ethnic groups, there are significant differences in the structure and nature of the relationship between polymorphic loci that determine the development of this disease. The results of the analysis of intergenic interactions demonstrate the significant role of polymorphic variants of genes *DRD2*, *COMT*, *RGS2*, *GRIN2B*, *GRM3*, *BDNF*, *NTRK3*, and *NXPH1* included in most statistically significant models.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare they have no conflict of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in the study involving people comply with the ethical standards of the institutional and/or national research ethics committee and the 1964 Helsinki Declaration and its subsequent changes or comparable ethical standards.

Informed consent was obtained from each of the participants in the study.

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