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HUMAN GENETICS

Genome-Wide Association Study of the Risk of Schizophrenia in the Republic of Bashkortostan

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Abstract—Genome-wide association studies (GWAS) have proven to be a powerful approach to discovering genes for susceptibility to schizophrenia; their findings are important not only for our understanding of the genetic architecture of a given disease, but also for potential applications in the field of personalized medicine. The aim of this work is to investigate the genetic risk factors for the development of schizophrenia during a genome-wide association study in the Republic of Bashkortostan.

Keywords: genetics, schizophrenia, genome-wide association study, ethnicity, Republic of Bashkortostan, international consortium on psychiatric genetics

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INTRODUCTION

More than 143 genome-wide association studies (GWAS) have been conducted worldwide on the risk of developing schizophrenia. The results of a number of GWAS studies have shown the presence of a significant genetic differentiation of populations according to polymorphic variants of genes associated with this disease [1, 2]. The largest genome-wide association study to date by PGC, an international consortium on psychiatric genetics, involving 76755 patients with schizophrenia and 243649 healthy individuals, identified 120 genes involved in such fundamental processes as synapse organization, neuronal differentiation, and neuronal transmission. Among them, the glutamate receptor subunit gene *GRIN2A*, transcription factor SP4, the gene of the constitutive coactivator of PPAR-gamma-like protein 1 *FAM120A*, the gene of the SA-1 cohesin subunits (SA1) *STAG1*, as well as a number of other rare destructive gene variants were found in patients with schizophrenia [3].

Recently, the largest whole exome sequencing (WES), involving 24248 schizophrenic patients and 97322 healthy individuals, identified ultra-rare mutations leading to the appearance of truncated protein forms in 32 genes, most of which are involved in the formation, structure, and function of synapses and are associated with a high risk of developing schizophrenia [4]. This finding points to synaptic dysfunction as a possible cause of schizophrenia. The identification of ultra-rare NMDA receptor subunit gene variants *GRIN2A* and *GRIA3* suggests impaired regulation of the glutamatergic system and the formation of inter-neuron synapses [4]. It is important to note that the last GWAS also identified the genes *STAG1*, *FAM120A*, *GRIN2A*, and *SP4* containing rare variants [4].

Thus, the convergence of common and rare gene variants associated with schizophrenia is supported by the fact that recent major GWAS and WES have identified a group of genes involved in similar biological processes, such as presynaptic and postsynaptic processes in excitatory and inhibitory neurons.

The purpose of this work is to study the genetic risk factors for the development of schizophrenia during a genome-wide association study in the Republic of Bashkortostan (Fig. 1).

MATERIALS AND METHODS

The objects of study were 437 men, 379 women (including 320 Russians, 357 Tatars, and 139 Bashkirs) diagnosed with paranoid schizophrenia (PS) F20.xx according to the International Classification of Diseases of the Tenth Revision (ICD-10), being treated at the Republican Clinical Psychiatric Hospital No. 1 of the Ministry of Health of the Republic of Bashkortostan. The mean age of the patients was 24.9 ± 8.9 years. The mean age of disease onset was 22.4 ± 7.3 years. Information on ethnicity up to the third generation was obtained by interviewing.

The control group consisted of 402 Russians, 383 Tatars, and 204 Bashkirs of the same age group, who were not registered with a psychiatrist and narcologist and denied having a burdened heredity for mental ill-

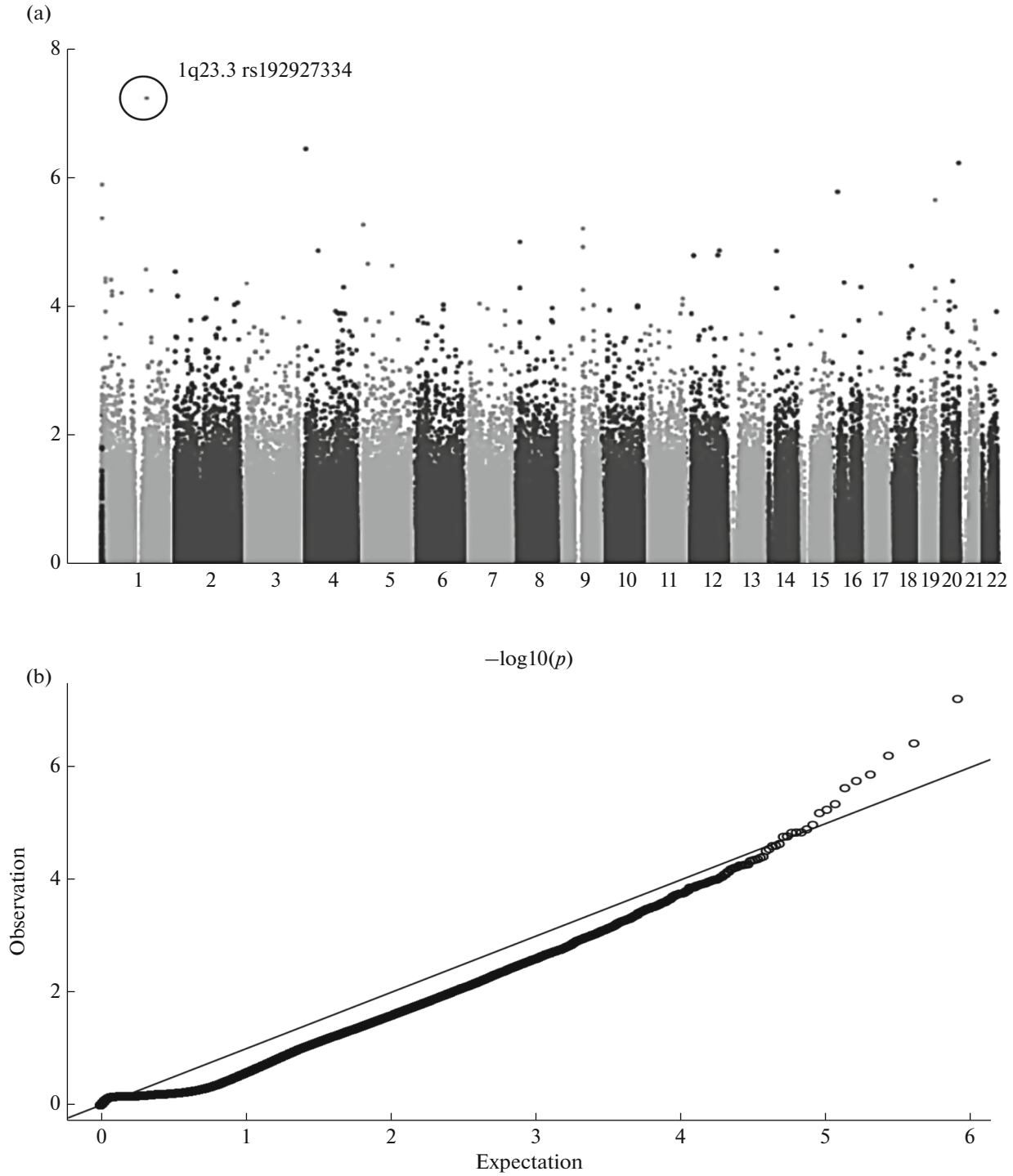

Fig. 1. Graphical representation of the results of a genome-wide association study of 395832 SNPs with paranoid schizophrenia (Manhattan plot). On the *X* axis, the chromosomal localization of SNPs is given; on the *Y* axis, the values of the negative decimal logarithm of the significance level *p* value (a); quantile–quantile plot (Q–Q plot). An illustration of assessing the presence of population stratification (b).

ness. The mean age of the healthy donors was 32.4 ± 12.4 years.

The independent sample of patients consisted of 190 individuals (68 Russian, 61 Tatar and 61 Bashkir ethnicity).

The independent control sample consisted of 238 healthy individuals: 95 Russians, 83 Tatars, and 60 Bashkirs.

DNA was isolated from peripheral blood by the standard phenol-chloroform extraction method [5].

The whole-genome genotyping of DNA samples was performed using the Illumina Human 610-Quad PsychChip, which included 610000 single-nucleotide polymorphic variants (SNPs).

A genome-wide association study of single-nucleotide polymorphic loci was performed using the PLINK 2.0 software package [6] at the Broad Institute at Harvard University within the framework of the ICPG [3].

Verifying the quality of DNA samples and progenotyped SNPs implied the exclusion from further analysis of DNA samples with a detected discrepancy between the designated and established sex during genotyping, as well as DNA samples in which more than 2% of the markers did not pass genotyping. Duplicate DNA samples and DNA samples of possible close relatives were identified and excluded based on an analysis of the proportion of identical alleles in different individuals and the proportion of alleles with a likely common origin. SNPs for which genotyping failed in more than 5% of individuals, SNPs with a rare allele frequency of less than 0.01, and SNPs with a statistically significant deviation (p = 1.0E-06) were excluded from the Hardy–Weinberg equilibrium. As a result of all stages of quality control and the adjustment of genetic stratification, 395832 single-nucleotide polymorphic variants were included in further analysis. The genome-wide significance level for this study was p = 1.26E-07.

To reduce the type-1 error correction FDR-BH (False Discovery Rate Benjamini-Hochberg) by the number of multiple comparisons [7].

The sample of patients and controls studied in this work is genetically heterogeneous, since it includes representatives of various ethnic groups (Russians, Tatars, and Bashkirs), which were formed on the basis of various populations of West Eurasian and East Eurasian origin. We applied a correction for the ethnic heterogeneity of the patient and control groups using the EIGENSTRAT method [8], since the mixed origin of the sample, the differences in allele frequencies of polymorphic markers between ethnic groups, and the different representation of individuals from different ethnic groups in the patient and control samples can lead to the random association of markers with the disease.

This method is based on calculation of the main components of genetic variability in the studied samples. Having established the axes of genetic variability of the sample, determined by the population structure, but not associated with the disease, the method allows for each marker to estimate its weight in determining one or another axis and thereby make an individual correction for each candidate marker. This minimizes the occurrence of false-positive associations due to the genetic heterogeneity of the sample and at the same time increases the likelihood of identifying significant associations.

RESULTS AND DISCUSSION

The results of a genome-wide association study of paranoid schizophrenia are shown in Fig. 1.

The highest level of association of paranoid schizophrenia was found with the polymorphic variant rs192927334 (p = 5.99E-08; p_{fdr} = 2.11E-03) localized in the intergenic space of the chromosome region 1q23.3. The gene *PBX1* is located in this region at a distance of 448316 kb from the polymorphic locus rs192927334 (Fig. 1).

Gene *PBX1* encodes a homeodomain-containing protein and is maximally expressed in the kidneys and brain of the fetus [9]. It is known that PBX1 proteins are able to interact with HOX proteins and are considered important HOX cofactors involved in the regulation of ontogeny genes [10–12]. In particular, Prep1 and PBX1 proteins form a triple complex with the Hoxb1 factor, which regulates gene expression in embryogenesis [10–13]. PBX proteins together with HOX have been shown to induce gene transcription *SHH*. The SHH protein is known to be essential for the development of various tissues during embryogenesis. The study of SHH function during neural tube and somite development has focused on its role in specification of the dorso-ventral polarity of these structures, but there is evidence that SHH has additional roles in cell survival and proliferation. Violations in SHH signaling following early dorsoventral specification of the cranial neural tube lead to increased cell death in both the neural tube and the neural crest. This indicates that SHH is constantly required as a trophic and mitogenic factor during brain development [14]. The knockout of both *Prep1* and *PBX1* leads to the death of mouse embryos at early stages of development [15, 16]. The reduced expression of *PBX1* in mesenchymal stromal cells isolated from adipose tissue leads to a significant increase in the ability to differentiate [17].

An analysis of the frequency distribution of genotypes of the rs192927334 polymorphic locus showed that the *rs192927334*C/C* genotype in patients with PS occurs with a higher frequency (98.78%) than in individuals of the control group (92.74%) (p = 8.3E-09; OR = 6.32; CI95% 3.24–12.33) (Tables 1 and 2). When introducing a correction for multiple comparisons to assess the proportion of false-positive results, carried out using the FDR (False Discovery Rate) method, the significance level p remained statistically significant (p_{fdr} = 4.68E-04) (Table 2). Genotype *rs192927334*A/C*, on the contrary, is more common in the control group: 7.26%, compared with 1.22% in patients. The odds ratio score (OR) for genotype *rs192927334*A/C* was 0.16 (CI95% 0.08–0.31), p = 8.3E-09; p_{fdr} = 5.85E-04 (Table 2). The frequency of homozygous genotype *rs192927334*A/A* was 0.00% in both patients and healthy people.

The frequency of meeting the allele *rs192927334*A* in patients with PS was significantly lower (0.61%)

Table 1. Single nucleotide polymorphic variants located in the 1q23.3 region and associated with paranoid schizophrenia

Gene	No. rs	SNP	Allele 1	Allele-1 frequency: patients, %	Allele-1 frequency: control, %	Allele 2	p	p_{fdr}
–	rs192927334	g.164146979C>A	*A*	0.0061	0.0363	*C*	5.99E-08	2.11E-03
PBX1	rs61803803	g.90024C>A	*A*	0.0196	0.0363	*C*	3.03E-03	0.884
–	rs10918018	g.164505021T>C	*C*	0.3556	0.3152	*T*	0.011	0.914
–	rs10753623	g.163744981T>C	*T*	0.4492	0.4099	*C*	0.014	0.924
–	rs4085003	g.164076924C>A	*C*	0.286	0.2518	*A*	0.019	0.930
–	rs7530102	g.163791020T>A	*A*	0.4221	0.4597	*T*	0.02	0.929
–	rs10753629	g.163769110T>G	*T*	0.4027	0.3666	*G*	0.021	0.929
PBX1	rs6672521	g.59759A>G	*G*	0.0863	0.1083	*A*	0.032	0.948
–	rs6656557	g.164209417G>A	*G*	0.4725	0.4386	*A*	0.035	0.957
–	rs10917897	g.164031874G>A	*G*	0.3756	0.4088	*A*	0.035	0.955
–	rs1745611	g.163686336C>T	*C*	0.451	0.4848	*T*	0.041	0.960
PBX1	rs1618566	g.83750G>A	*A*	0.2506	0.2805	*G*	0.047	0.962
–	rs1416261	g.164478592C>T	*T*	0.4578	0.424	*C*	0.047	0.962

than in the control group of individuals: 3.63% (p = 5.99E-08; p_{fdr} = 2.11E-03). The OR indicator for the development of PS for the allele *rs192927334*A* was 0.16 (CI95% 0.08–0.31); for the allele *rs192927334*C*, it was 6.12 (CI95% 3.15–11.9) (Table 2).

The prevalence of the allele *rs192927334*A* in healthy individuals (3.63%) was similar to that in individuals of European origin: Finns (3.0%), English (1.6%), and also Americans of Mexican ancestry (1.6%) (Table 3).

Taking into account the ethnic heterogeneity of the patient and control samples studied by us, we also analyzed the association of the polymorphic locus rs192927334, localized in the 1q23.3 region, with PS, taking into account the ethnicity of individuals, to assess the effectiveness and reliability of the genome-wide association study in the combined group of patients with PS and healthy individuals adjusted for population heterogeneity.

The most pronounced association of PS with SNP rs192927334, localized in the 1q23.3 region, was found in Russians. As in the analysis of the association of the combined group of patients and controls, SNP rs192927334 was associated with the highest level of significance (Table 2). The frequency of the allele *rs192927334*A* in Russian patients with PS (0.31%) was significantly lower than in healthy people (4.23%) (p = 2.4E-04; OR = 0.07; CI95% 0.02–0.29); however, after the introduction of the FDR correction, the differences turned out to be statistically insignificant (p_{fdr} = 0.999) (Table 2).

By analyzing the association of SNP rs192927334 with PS in Tatars, we also found statistically significant differences between the groups of patients and the control (Table 2). The rs192927334 polymorphic locus was associated with the level of significance p = 4.4E-04. The OR score for the allele *rs192927334*A*, determined with a frequency of 0.56% in patients and 3.52% in the control group, was 0.15 (CI95% 0.05–0.43); however, after introduction of the FDR correction, the differences turned out to be statistically insignificant (p_{fdr} = 0.999) (Table 2).

The allele *rs192927334*A* in patients with PS of Bashkir ethnicity was also less common than in the control group (1.44% vs. 2.71%), but the differences were not significant (p = 0.267; p_{fdr} =0.968) (Table 2).

Within the framework of the 1000 Genomes project, genotyping of the polymorphic locus rs192927334 was carried out in a number of populations of the world (Table 3). The allele frequencies of the polymorphic locus rs192927334 in the populations of the Volga-Ural region are similar to those in Finns (Tables 2 and 3).

Thus, when analyzing the association of SNP rs192927334 (1q23.3), taking into account the ethnicity of individuals, it was shown that the association that we established with a genome-wide level of significance in the combined group of patients and controls is observed with varying degrees of severity when analyzing the association in individual ethnic groups: Russians, Tatars, and Bashkirs, which corresponds to the data of other studies, according to which this chromosomal region is associated with schizophrenia in populations of Caucasian and Asian origin [18–25].

To confirm the results of genome-wide analysis, a replicative association analysis was performed for an independent sample (Table 4).

The frequency distribution of SNP rs192927334 genotypes in the combined independent sample of patients and controls of different ethnicity corre-

Table 2. Frequency distribution of genotypes and alleles of the polymorphic variant rs192927334 in samples of patients with paranoid schizophrenia and in control groups of different ethnicity

Genotype/ allele	Patients		Control		p	p_{fdr}	OR (CI95%)
	n_i	$p_i \pm s_p$, CI95%	n_i	$p_i \pm s_p$, CI95%			
In total							
A/A	0	–	0	–	–	–	–
A/C	10	1.22 ± 0.38 0.59–2.24	72	7.26 ± 0.82 5.72–9.05	8.3E-09	5.85E-04	0.16 (0.08–0.31)
C/C	807	98.78 ± 0.38 97.76–99.41	920	92.74 ± 0.82 90.95–94.28	8.3E-09	4.68E-04	6.32 (3.24–12.33)
A	10	0.61 ± 0.19 0.29–1.12	72	3.63 ± 0.42 2.85–4.55	5.99E-8	2.11E-03	0.16 (0.08–0.31)
C	1624	99.39 ± 0.19 98.88–99.71	1912	96.37 ± 0.42 95.45–97.15	5.99E-8	2.11E-03	6.12 (3.15–11.9)
Russians							
A/A	0	–	0	–	–	–	–
A/C	2	0.62 ± 0.44 0.08–2.24	34	8.46 ± 1.39 5.93–11.62	3.6E-06	0.999	0.07 (0.02–0.29)
C/C	318	99.38 ± 0.44 97.76–99.92	368	91.54 ± 1.39 88.38–94.07	3.6E-06	0.508	14.69 (3.5–61.63)
A	2	0.31 ± 0.22 0.04–1.12	34	4.23 ± 0.71 2.95–5.86	2.4E-04	0.999	0.07 (0.02–0.29)
C	638	99.69 ± 0.22 98.88–99.96	770	95.77 ± 0.71 94.14–97.05	2.4E-04	0.999	14.09 (3.37–58.88)
Tatars							
A/A	0	–	0	–	–	–	–
A/C	4	1.12 ± 0.56 0.31–2.84	27	7.05 ± 1.31 4.7–10.09	5.7E-05	0.999	OR = 0.15 (0.05–0.43)
C/C	353	98.88 ± 0.56 97.16–99.69	356	92.95 ± 1.31 89.91–95.3	5.7E-05	0.947	OR = 6.69 (2.32–19.32)
A	4	0.56 ± 0.28 0.15–1.43	27	3.52 ± 0.67 2.34–5.09	4.4E-04	0.999	OR = 0.15 (0.05–0.43)
C	710	99.44 ± 0.28 98.57–99.85	739	96.48 ± 0.67 94.91–97.66	4.4E-04	0.999	OR = 6.49 (2.26–8.64)
Bashkirs							
A/A	0	–	0	–	–	–	–
A/C	4	2.88 ± 1.42 0.79–7.2	11	5.42 ± 1.59 2.74–9.49	0.260	0.966	–
C/C	135	97.12 ± 1.42 92.8–99.21	192	94.58 ± 1.59 90.51–97.26	0.260	0.966	–
A	4	1.44 ± 0.71 0.39–3.64	11	2.71 ± 0.81 1.36–4.8	0.267	0.968	–
C	274	98.56 ± 0.71 96.36–99.61	395	97.29 ± 0.81 95.2–98.64	0.267	0.968	–

Note (for Tables 2 and 4). n_i is number of groups; p_i is the allele (genotype) frequency.

Table 3. Distribution of allele frequencies of the polymorphic variant rs192927334 in different populations according to the 1000 Genomes project

Population	Abbreviation	Allele frequency *A*, %	Allele frequency *C*, %
Chinese	CDX/CHB	0.0000	100.0
Europeans (North/West)	CEU	1.52	98.48
Finns	FIN	3.03	96.97
English	GBR	1.65	98.35
Mexicans	MXL	1.56	98.44
Africans	ACB	0.0000	100.0
Japanese	JPT	0.0000	100.0

sponded to the Hardy–Weinberg distribution (Table 4). The frequencies of alleles and genotypes of SNP rs192927334 in this independent sample of patients with PS and controls were similar to those in the initially studied groups. The allele *rs192927334*C* was met with a higher frequency in patients with PS: 99.2% compared with 96.82% in the control group ($p = 0.017$; OR = 4.06 (CI95% 1.17–14.13) (Table 4).

The distribution of frequencies of genotypes and alleles of the polymorphic variant rs192927334 in individual ethnic groups of Russians, Tatars, and Bashkirs of the independent sample was similar to that in the initially studied groups. However, no association of the polymorphic locus rs192927334 with PS was found in the ethnic groups of Russians, Tatars, and Bashkirs (Table 4).

Thus, the results of the replicative study confirm the data obtained in the course of genome-wide analysis on the association of SNP rs192927334, localized in the chromosomal region 1q23.3, with the development of paranoid schizophrenia in Russians, Tatars, and Bashkirs.

Published data on the study of the association of SNP rs192927334 with paranoid schizophrenia, mental illness, and other multifactorial diseases were not found.

Nevertheless, the results of a number of studies demonstrate the involvement of polymorphic variants of the genes of this chromosomal region in the development of schizophrenia (*RGS4* [20], *UHMK1* [21], *NOSIAP1* [26]), other mental illnesses, and disorders of neuronal development. Thus, the involvement of SNPs in the chromosome region 1q23-25 with the development of schizophrenia in 1236 Chinese people was confirmed [23]. Another genome-wide study found an association of two SNPs rs10218843 (p = 3.04E-07) and rs11265461 (p = 1.94E-07) of a gene encoding a family of proteins that transmit a signal about the activation of the lymphocyte molecule family member 1 (*SLAMF1*) located in the chromosome region 1q23.3 with treatment-resistant schizophrenia in 795 patients and 806 healthy Chinese people [24]. In addition, GWAS identified an association of SNPs rs1289726 (p = 2.0E-04) located at a distance of 297 kb from the gene *PBX1* (1q23.3), with schizophrenia in Europeans [22]. The connection of chromosomal region 1q23 to schizophrenia in British and Icelandic families was demonstrated in GWAS [18].

The association of allele *rs2275558*A* of the gene *PBX1* with susceptibility to obsessive-compulsive disorder both in a general sample of Brazilians and in a sample of men was established [27].

GWAS in European and African-American populations confirmed the association of the SNP rs4657247 gene *RGS5* lying in the region 1q23.3, with the development of bipolar disorder [28]. The GWAS study by J. Namkung et al. [29] confirmed the previously obtained results of the work of K. Chowdari, which showed a link between the chromosomal region 1q23.3 and the risk of developing schizophrenia in Indians and individuals of European origin [19], revealing the association of the polymorphic marker tsc1457991-tsc1254625 of the gene *PBX1* with alcoholism in 668 alcoholics and 285 healthy individuals of Korean ethnicity [29]. Deletion of the chromosomal region 1q23.3 (1.871 Mb) leads to the syndrome of congenital anomalies of the kidneys and urinary tract (CAKUT), which is characterized by autism, schizophrenia, epilepsy, and intellectual impairment that manifest themselves at a later age [30–32].

Thus, as a result of this study, we found an association of the single-nucleotide polymorphic variant rs192927334 located at a distance of 448316 kb from the gene *PBX1* in the chromosomal region 1q23.3, which is linked to a risk of developing schizophrenia and other mental illnesses, according to a number of studies with the development of paranoid schizophrenia in three ethnic groups: Russians, Tatars and Bashkirs living in the Republic of Bashkortostan. This may indicate the likely involvement of the gene *PBX1* in the pathogenesis of schizophrenia. Especially considering that this gene encodes a transcription factor that promotes protein-to-protein interaction and plays a decisive role in a number of developmental processes, including the formation of brain structures.

Table 4. Frequency distribution of genotypes and alleles of the polymorphic variant rs192927334 in an independent sample of patients with paranoid schizophrenia and in control groups of different ethnicity

Genotype/allele	Patients		Control		p	OR (CI95%)
	n_i	$p_i \pm s_p$, CI95%	n_i	$p_i \pm s_p$, CI95%		
In total						
A/A	0	–	0	–	–	–
A/C	3	1.6 ± 0.92 0.33–4.62	15	6.36 ± 1.59 3.6–10.27	0.016	0.24 (0.07–0.84)
C/C	184	98.4 ± 0.92 95.38–99.67	221	93.64 ± 1.59 89.73–96.4	0.016	4.16 (1.19–14.59)
A	3	0.8 ± 0.46 0.17–2.33	15	3.18 ± 0.81 1.79–5.19	0.017	0.25 (0.07–0.87)
C	371	99.2 ± 0.46 97.67–99.83	457	96.82 ± 0.81 94.81–98.21	0.017	4.06 (1.17–14.13)
H-W		0.229 (0.632)		0.254 (0.614)		
Russians						
A/A	0	–	0	–	–	
A/C	1	1.49 ± 1.48 0.04–8.04	5	5.32 ± 2.31 1.75–11.98	0.402	
C/C	66	98.51 ± 1.48 91.96–99.96	89	94.68 ± 2.31 88.02–98.25	0.402	
A	1	0.75 ± 0.75 0.02–4.09	5	2.66 ± 1.17 0.87–6.1	0.407	
C	133	99.25 ± 0.75 95.91–99.98	183	97.34 ± 1.17 93.9–99.13	0.407	
Tatars						
A/A	0	–	0	–	–	
A/C	1	1.69 ± 1.68 0.04–9.09	6	7.23 ± 2.84 2.7–15.07	0.239	
C/C	58	98.31 ± 1.68 90.91–99.96	77	92.77 ± 2.84 84.93–97.3	0.239	
A	1	0.85 ± 0.85 0.02–4.63	6	3.61 ± 1.45 1.34–7.7	0.245	
C	117	99.15 ± 0.85 95.37–99.98	160	96.39 ± 1.45 92.3–98.66	0.245	
Bashkirs						
A/A	0	–	0	–	–	
A/C	1	1.64 ± 1.63 0.04–8.8	4	6.78 ± 3.27 1.88–16.46	0.203	
C/C	60	98.36 ± 1.63 91.2–99.96	55	93.22 ± 3.27 83.54–98.12	0.203	
A	1	0.82 ± 0.82 0.02–4.48	4	3.39 ± 1.67 0.93–8.45	0.207	
C	121	99.18 ± 0.82 95.52–99.98	114	96.61 ± 1.67 91.55–99.07	0.207	

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COMPLICANCE WITH ETHICAL STANDARDS

Conflict of interest. The author declares that she has no conflicts of interest.

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

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

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