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HUMAN GENETICS

Genome-Wide Association Study: Analysis of Association of Polymorphic Loci in 4p15.2 and 20q13.31 Regions with Paranoid Schizophrenia

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Abstract—Over fifteen years, genome-wide association studies (GWAS) have identified several million polymorphic risk markers for schizophrenia, significantly advancing our understanding of the genetic architecture of schizophrenia. The aim of this study was to study genetic risk factors for the development of schizophrenia in a genome-wide association analysis in Russians, Tatars, and Bashkirs from the Republic of Bashkortostan. The studied sample consisted of 816 patients with paranoid schizophrenia and 989 healthy individuals. GWAS genotyping of DNA samples was carried out on the PsychChip, which included 610000 single nucleotide polymorphic variants (SNPs). As a result of the study, for the first time, an association of SNPs rs73254185 (4p15.2) and rs587778384 of the *GNAS* gene (20q13.31) with the risk of paranoid schizophrenia in individuals of different ethnicity, Russians, Tatars, and Bashkirs living in the Republic of Bashkortostan, was established, which probably may indicate involvement of the *PI4K2B* and *GNAS* genes localized in these chromosomal regions in the pathogenesis of schizophrenia.

Keywords: genetics, schizophrenia, genome-wide association analysis, ethnicity, Republic of Bashkortostan, Psychiatric Genomics Consortium

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INTRODUCTION

Schizophrenia is a complex and often chronic mental disorder with a high heredity. Schizophrenia is still diagnosed clinically on the basis of psychiatric symptoms; there are currently no diagnostic tests or biomarkers available. A pathophysiology-based diagnostic and treatment regimen is also not available. Elucidation of the pathogenesis is necessary for the development of diagnostic and treatment approaches.

Over the past few decades, genetic research has greatly advanced our understanding of the genetic architecture of schizophrenia. Large-scale genetic studies have shown that both rare and common genetic variants play an important role in the development of this disease [1, 2].

A number of GWAS studies have been conducted in different ethnic groups: Indians [3], African Americans [4], Hispanics [5], and Japanese [6]. However, most large-scale GWAS studies of schizophrenia have been conducted in samples of European origin. The results established in one population are not always reproduced in others, which is one of the main problems in conducting GWAS. The reasons for this phenomenon may, firstly, be the insufficient statistical power of the replicative sample. Another reason is different allele frequencies and the structure of linkage disequilibrium in populations. A GWAS study conducted in 2019 on a sample of East Asian origin established an association of three chromosome regions, which was also found in Europeans. However, the association of other 14 single nucleotide polymorphic variants (SNP) with schizophrenia was found only in the Chinese [7]. These data point to the existence of both common and ethnospecific risk markers for schizophrenia.

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

MATERIALS AND METHODS

The object of study was 437 men and 379 women (320 Russians, 357 Tatars, 139 Bashkirs) diagnosed with paranoid schizophrenia (PS)—F20.xx—according to the international classification of diseases of the tenth revision (ICD-10) being treated in the Republican Clinical Psychiatric Hospital No. 1 of the Ministry of Health of the Republic of Bashkortostan. The

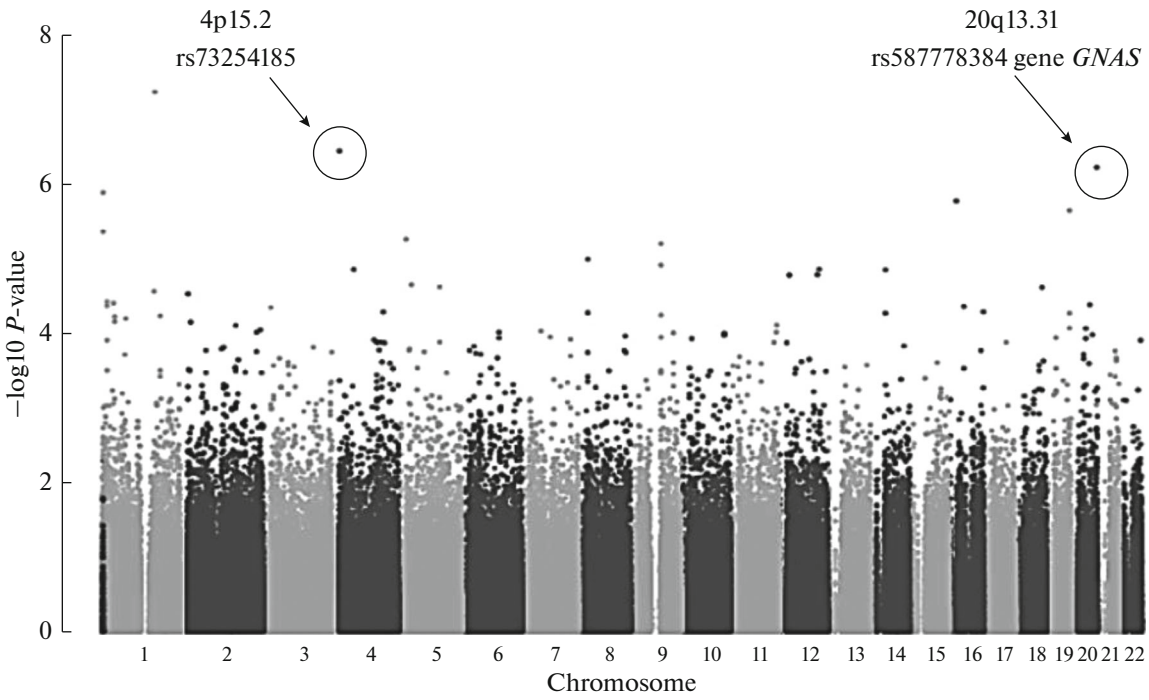

Fig. 1. Graphical representation of the results of a genome-wide analysis of the association of 395832 SNPs with paranoid schizophrenia (Manhattan plot). The *x* axis indicates the chromosomal location of SNPs; the *y* axis indicates the values of the negative decimal logarithm of the significance level *P*-value.

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 through a survey. The control group consisted of 402 Russians, 383 Tatars, 204 Bashkirs of the same age group, who were not registered with a psychiatrist and narcologist and denied having a burdened heredity for mental illness. The mean age of healthy donors was 32.4 ± 12.4 years.

Genome-wide genotyping of DNA samples was performed on the Illumina Human 610 Quad Beadchip biochip, which includes 610000 SNPs at the Broad Institute at Harvard University as part of the International Psychiatric Genomics Consortium. A genome-wide analysis of the association of single nucleotide polymorphic loci was performed using the PLINK 2.0 software package [8].

Checking the quality of DNA samples and progenotyped SNPs implied 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 on the basis of the analysis of the proportion of identical alleles in different individuals, as well as the proportion of alleles with a likely common origin. SNPs for which more than 5% of individuals failed to be genotyped, SNPs with a rare allele frequency of less than 0.01, and SNPs with a statistically significant deviation were excluded (p = 1.0E-06) from the Hardy–Weinberg equilibrium. As a result of conducting all stages of quality control and 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 I error, the FDR-BH (False Discovery Rate Bengamini-Hochberg) correction for the number of multiple comparisons was applied [9].

The samples of patients and controls in this work are genetically heterogeneous, since they include 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 ethnic heterogeneity of patient and control groups using the EIGENSTRAT method [10], since the mixed origin of the sample, differences in allele frequencies of polymorphic markers between ethnic groups, and the different representation of individuals from different ethnic groups in patient and control samples can lead to random association of markers with a disease. This method is based on the 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 makes it possible for each marker to estimate its weight in determining a particular axis and thereby make an individ-

Table 1. Single nucleotide polymorphic variants located in the 4p15.2 region and associated with paranoid schizophrenia

Gene	No. of rs	SNP	Allele 1	Frequency of allele 1		Allele 2	p	p_{fdr}	OR
				patients, %	control, %				
LOC105374536	rs73254185	g.25458395G>A	*A*	0.00618	0.03309	*G*	3.70E-07	0.012	0.174
LOC105374536	rs6852016	g.25440525G>A	*A*	0.2974	0.3459	*G*	1.76E-03	0.856	0.794
–	rs12502737	g.25066802A>C	*C*	0.4541	0.498	*A*	3.59E-03	0.884	0.821
LOC105374536	rs10008104	g.25444762G>A	*A*	0.2907	0.3348	*G*	4.41E-03	0.891	0.811
–	rs7654693	g.25066309T>G	*G*	0.2699	0.3046	*T*	0.018	0.957	0.838
–	rs759245	g.25058232A>G	*G*	0.4137	0.3802	*A*	0.038	0.991	1.154

ual correction for each candidate marker. This minimizes the occurrence of false positive associations and at the same time increases the likelihood of identifying significant associations.

RESULTS AND DISCUSSION

Analysis of the Association of Paranoid Schizophrenia with Polymorphic Loci Located in the 4p15.2 Region

This genome-wide analysis revealed a number of polymorphic loci associated with PS with a significance level of order p = 3.70E-07, which with a high degree of probability may be involved in the formation of a hereditary predisposition to paranoid schizophrenia (Fig. 1, Table 1). These loci are localized in the 4p15.2 region. One of them, rs73254185, is localized on the short arm of chromosome 4 in the intron region of the gene encoding RNA (*LOC105374536*), function which is not yet known.

According to the 1000 Genomes Project, the frequency of allele *rs73254185*A* varies in populations around the world. Thus, allele *rs73254185*A* is least common in populations of European origin (CEU 1.5%); in African populations, its frequency is higher (AFR 4.5%), but most often the allele occurs in populations of Chinese origin (CHB 7.8%) (http://www.ensembl.org/Homo_sapiens/Variation/Population).

The closest gene located at a distance of about 178 kb from this polymorphic locus rs73254185 is the gene *PI4K2B*. *PI4K2B* encodes the enzyme phosphatidylinositol-4-kinase, a member of phosphoinositide (PI) of the signaling pathway; it consists of ten exons and has a length of about 45 kb. The main function of the phosphatidylinositol-4-kinase enzyme is to phosphorylate phosphatidylinositol and convert it to phosphatidylinositol-4-phosphate. In this gene, 397 SNPs have been identified. Data from recent investigations indicate the involvement of the phosphoinositide signaling pathway in the pathogenesis of schizophrenia, bipolar disorder, and other mental illnesses. This is associated with its influence on the regulation of the actin cytoskeleton and the formation of dendritic spines and the development of synapses in the nervous tissue [11]. *PI4K2B* is associated with attention deficit hyperactivity disorder (ADHD) and neuronal migration anomalies [12].

Research over the past 15 years has clearly shown that PI4P itself is a regulatory lipid that functions in the Golgi apparatus and in endosomal membranes, where it controls vesicular transport [13]. This paradigm-shifting discovery placed PI4P at the center of the lipid homeostatic cellular machinery. Studies in mice have shown severe defects in Schwann cell myelination in PI4KA and PI4KB knockouts, as well as spinocerebellar degeneration in knockouts of gene *PI4K2A* [14, 15]. Evidence of changes in molecules associated with PI in the postmortem prefrontal cortex in patients with schizophrenia has been obtained [11]. In light of this, a common thread between PI4K enzymes is their critical involvement in the creation of the lipid landscape of mammalian cells, especially in neuronal development and plasticity [16]. Animal and human genetic studies suggest a vital role for PI4K enzymes in the development and function of various organs, including the nervous system [11, 16].

An analysis of the frequency distribution of genotypes and alleles of the polymorphic locus rs73254185 showed that the genotype *rs73254185*G/G* in patients with PS occurs with a higher frequency (98.76%) than in individuals of the control group (93.38%) (p = 1.6E-08; OR = 5.66, CI95% = 2.86–12.45). 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} = 6.45E-04. Genotype *rs73254185*A/G*, on the contrary, is more common in the control group—in 6.62% of cases compared with 1.24% of patients. The odds ratio score for genotype *rs73254185*A/G* was 0.18 (CI95% = 0.08–0.35, p = 1.6E-08; p_{fdr} = 7.52E-04). The frequency of homozygous genotype *rs73254185*A/A* was 0.00% in both patients and healthy people (Table 2).

Allele *rs73254185*G*, determined with a frequency of 99.38% in patients and 96.69% in the control group, is a marker of an increased risk of developing PS (p = 1.37E-07; p_{fdr} = 0.0116; OR = 5.5, CI95% = 2.79–

Table 2. Frequency distribution of genotypes and alleles of polymorphic variants rs73254185 and rs587778384 of gene *GNAS* in samples of patients with paranoid schizophrenia and in control groups of different ethnicity

	rs73254185					rs587778384				
Genotype/ alleles	*A/A*	*A/G*	*G/G*	*A*	*G*	*T/T*	*T/C*	*C/C*	*T*	*C*
Total										
Patients, *n*	0	10	799	10	1608	0	5	807	5	1619
	$p_i \pm s_p$ CI (%)									
	–	1.24 ± 0.39 0.59–2.26	98.76 ± 0.39 97.74–99.41	0.62 ± 0.2 0.3–1.13	99.38 ± 0.2 98.87–99.7	–	0.62 ± 0.28 0.2–1.43	99.38 ± 0.28 98.57–99.8	0.31 ± 0.14 0.1–0.72	99.69 ± 0.14 99.28–99.9
Control, *n*	0	64	903	64	1870	0	59	924	59	1907
	–	6.62 ± 0.8 5.13–8.37	93.38 ± 0.8 91.63–94.87	3.31 ± 0.41 2.56–4.21	96.69 ± 0.41 95.79–97.44	–	6 ± 0.76 4.6–7.67	94 ± 0.76 92.33–95.4	3 ± 0.38 2.29–3.85	97 ± 0.38 96.15–97.71
p	–	1.6E-08	1.6E-08	3.7E-07	3.7E-07	–	2.0E-09	2.0E-09	6.13E-07	6.13E-07
p_{fdr}	–	7.52E-04	6.45E-04	0.012	0.012	–	2.82E-04	1.82E-04	0.017	0.017
OR (CI95%)	–	0.18 (0.08–0.35)	5.66 (2.86–12.45)	0.18 (0.08–0.36)	5.5 (2.79–12.06)	–	0.1 (0.04–0.25)	10.31 (4.12–25.81)	0.1 (0.04–0.25)	10.02 (4.01–25.03)
Russians										
Patients, *n*	0	4	312	4	628	0	0	318	0	636
	–	1.27 ± 0.63 0.35–3.21	98.73 ± 0.63 96.79–99.65	0.63 ± 0.31 0.17–1.61	99.37 ± 0.31 98.39–99.83	0	0	100.0	0	100.0
Control, *n*	0	30	361	30	752	0	26	371	26	768
	–	7.67 ± 1.35 5.24–10.77	92.33 ± 1.35 89.23–94.76	3.84 ± 0.69 2.6–5.43	96.16 ± 0.69 94.57–97.4	–	6.55 ± 1.24 4.32–9.45	93.45 ± 1.24 90.55–95.68	3.27 ± 0.63 2.15–4.76	96.73 ± 0.63 95.24–97.85
p	–	7.5E-05	7.5E-05	5.1E-04	5.1E-04	–	8.7E-06	8.7E-06	8.1E-03	8.1E-03
p_{fdr}	–	0.999	0.96	0.999	0.999	–	0.819	0.614	1.354	1.354
OR (CI95%)	–	0.15 (0.05–0.43)	6.48 (2.26–18.6)	0.16 (0.06–0.46)	6.26 (2.19–17.86)	–	0.02 (0–0.15)	45.44 (6.14–336.28)	0.02 (0–0.15)	43.9 (5.95–323.97)

Table 2. (Contd.)

	rs73254185					rs587778384				
Genotype/ alleles	*A/A*	*A/G*	*G/G*	*A*	*G*	*T/T*	*T/C*	*C/C*	*T*	*C*
Tatars										
Patients, *n*	0	3	352	3	707	0	1	354	1	709
	–	0.85 ± 0.49 0.17–2.45	99.15 ± 0.49 97.55–99.83	0.42 ± 0.24 0.09–1.23	99.58 ± 0.24 98.77–99.91	–	0.28 ± 0.28 0.01–1.56	99.72 ± 0.28 98.44–99.99	0.14 ± 0.14 0–0.78	99.86 ± 0.14 99.22–100
Control, *n*	0	21	351	21	723	0	22	357	22	736
	–	5.65 ± 1.2 3.53–8.5	94.35 ± 1.2 91.5–96.47	2.82 ± 0.61 1.76–4.28	97.18 ± 0.61 95.72–98.24	–	5.8 ± 1.2 3.67–8.66	94.2 ± 1.2 91.34–96.33	2.9 ± 0.61 1.83–4.36	97.1 ± 0.61 95.64–98.17
p	–	2.9E-04	2.9E-04	1.7E-03	1.7E-03	–	4.5E-05	4.5E-05	2.64E-03	2.64E-03
p_{fdr}	–	0.999	0.999	0.942	0.942	–	0.999	0.977	0.945	0.945
OR (CI95%)	–	0.14 (0.04 –0.47)	7.02 (2.08–23.75)	0.15 (0.04–0.51)	6.85 (2.03–23.07)	–	0.05 (0.01–0.37)	21.82 (2.93–162.76)	0.05 (0.01–0.37)	21.19 (2.85–157.63)
Bashkirs										
Patients, *n*	0	3	134	3	271	0	4	134	4	272
	–	2.19 ± 1.25 0.45–6.27	97.81 ± 1.25 93.73–99.55	1.09 ± 0.63 0.23–3.17	98.91 ± 0.63 96.83–99.77	–	2.9 ± 1.43 0.8–7.26	97.1 ± 1.43 92.74–99.2	1.45 ± 0.72 0.4–3.67	98.55 ± 0.72 96.33–99.6
Control, *n*	0	13	187	13	387	0	11	192	11	395
	–	6.5 ± 1.74 3.51–10.86	93.5 ± 1.74 89.14–96.49	3.25 ± 0.89 1.74–5.49	96.75 ± 0.89 94.51–98.26	–	5.42 ± 1.59 2.74–9.49	94.58 ± 1.59 90.51–97.26	2.71 ± 0.81 1.36–4.8	97.29 ± 0.81 95.2–98.64
p	–	0.068	0.068	0.082	0.082	–	0.398	0.398	0.273	0.273
p_{fdr}	–	0.903	0.903	0.908	0.908	–	0.981	0.981	0.968	0.968
OR (CI95%)	–	–	–	–	–	–	–	–	–	–

n—group size, p_{fdr}—allele (genotype) frequency, sp—error of p_i, CI95%—confidence interval, *p*—significance level, χ^2 (*P*)—Hardy–Weinberg equilibrium in the studied groups.

12.06). Allele *rs73254185*A*, correspondingly, is a marker of reduced risk (OR = 0.18, CI95% = 0.08–0.36) (Table 2). An analysis of the frequency distribution of genotypes and alleles of SNP rs73254185, localized in the 4p15.2 region, in patients and individuals of control groups of different ethnicity showed the presence of pronounced differences between the comparison groups of Russians and Tatars (Table 2).

The most pronounced association of PS with rs73254185 localized in the 4p15.2 region was found in Russians. In this case, the frequency of allele *rs73254185*A* in Russian patients with PS (0.63%) was significantly lower than in healthy patients (3.84%) (p = 5.1E-04; OR = 0.16, CI95% = 0.06–0.46). However, after adjusting for FDR multiple comparisons, these differences were not statistically significant ($p_{fdr} = 0.999$) (Table 2). Analyzing the association of SNP rs73254185 with PS in Tatars, we found statistically significant differences between groups of patients and controls with a significance level p = 1.77E-03. The odds ratio score for allele *rs73254185*A*, determined with a frequency of 0.42 in patients and 2.82% in the control, was 0.14 (CI95% = 0.04–0.47). After the introduction of the FDR correction, the differences were not statistically significant ($p_{fdr} = 0.942$). In patients with PS of the Bashkirs, the allele *rs73254185*A* was also less common than in the control group (1.09% vs. 3.25%), but the differences were not significant ($p = 0.082$; $p_{fdr} = 0.908$) (Table 2).

Thus, when analyzing the association of the polymorphic variant of the 4p15.2 region 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 control is also observed with varying degrees of severity in certain ethnic groups—Russians, Tatars, and Bashkirs, which is consistent with data from other studies, according to which this chromosomal region is associated with schizophrenia in populations of Caucasian and Asian origin [17–21].

Published data on the study of the association of the rs73254185 polymorphic locus with paranoid schizophrenia, mental illness, and other multifactorial diseases were not found. However, to date, there are a number of works that have studied the association of SNPs located in the 4p15.2 region with schizophrenia and other mental illnesses in various populations. Linkage of the chromosome region 4p15-p16 with bipolar disorder and major depressive disorder has been established with a high level of significance in Scottish families [22], as well as schizophrenia and bipolar disorder in Europeans [20]. Haplotype analysis revealed an association of a 20 Mb region in chromosome region 4p15.2 with familial cases of schizophrenia and schizoaffective disorder in the Welsh [17, 19], as well as in a large group of Ashkenazi Jews with a familial case of bipolar disorder and schizophrenia [18]. Associations with a high level of significance were established number of genes in chromosomal 4p15.2 region: *KIAA0746*, *CCKAR*, and *DKFZp761B107*—with schizophrenia and bipolar disorder in Scots [19]; *CCKAR*—in Chinese, Japanese, and Spaniards [23]; *PI4K2B*—in cannabis-addicted Europeans and African Americans [24].

In addition, it was found that SNP rs10939038, which is a potentially important genetic marker for the risk of developing schizophrenia, is in strong linkage disequilibrium with polymorphic markers of the gene *PI4K2B*; this group of researchers hypothesized that *PI4K2B* is an important candidate gene for schizophrenia [19]. The association of a haplotype consisting of two SNPs (rs10939038rs17408391) located in the chromosomal region of the gene *PI4K2B* (4p15.2) with schizophrenia in Scots was shown, which again demonstrates the possible involvement of the gene *PI4K2B* in the etiopathogenesis of schizophrenia [25] and also confirms the data of earlier studies [17]. A genome-wide study found an association of SNP rs17390445 (in the 4p15 region) with the efficacy of the atypical antipsychotic ziprasidone in Europeans [21].

In addition, an association of the chromosomal region 4p15.2 with the development of motor alalia in children with autism spectrum disorders was established [26]. A connection between a microdeletion in the 4p15.2 region and the development of Axenfeld–Rieger syndrome, characterized by developmental delay, was shown [27]. It was revealed that *de novo* 4p15.2 duplication can lead to global developmental delay and cognitive impairment [28].

Analysis of the Association of Paranoid Schizophrenia with Polymorphic Loci Located in the 20q13.31 Region

A genome-wide study of the combined group of patients and control also revealed a pronounced association of PS with single-nucleotide polymorphic loci localized in the 20q13.31 region (Fig. 1, Table 3). SNP rs587778384 showed the highest level of association with the disease among the loci in this region (p = 6.13E-07), located on the long arm of chromosome 20 in the region q13.31 in the intron region of the gene *GNAS*. Gene *GNAS* consists of 13 exons and covers about 71 kb of genomic DNA. Currently, in the gene *GNAS*, 646 SNPs have been identified. It is known that the gene *GNAS* imprints an expression pattern of multiple transcripts, including the alpha subunit of the guanine-stimulating nucleotide-binding protein (Gαs), extra-large Gαs (XLαs), and neuroendocrine secretory protein NESP55 [29]. In addition to this, there are two additional A/B, or (1A or 1'), and the GNAS antisense transcript (GNAS-AS1), which are noncoding, although there are suggestions that the A/B transcript can be translated [30].

Among the many different mechanisms involved in the etiology of schizophrenia, the results of several studies support the suggestion that dysregulation of

Table 3. SNPs located at 20q13.31 and associated with paranoid schizophrenia

Gene	No. of rs	SNP	Allele 1	Frequency of allele *T*, patients, %	Frequency of allele *A*, control, %	Allele 2	*p*	p_{fdr}	OR
GNAS	rs587778384	g.20064C>T	*T*	0.0031	0.03001	*C*	6.13E-07	0.017	0.097
–	rs6015320	g.57205047G>A	*A*	0.386	0.43	*G*	0.0072	0.900	0.830

neurotransmitter signal transduction and increased vulnerability to apoptosis [31, 32] may play a role in the pathological biology of this disease. In this case, heterotrimeric guanine nucleotide-binding proteins, known as G proteins, may provide an intriguing link between the signal transduction hypothesis and the apoptosis hypothesis of schizophrenia development [33]. Changes in the intracellular G-protein signaling pathway have been found in patients with schizophrenia, and G proteins are also known to be used as biochemical markers for diagnosing schizophrenia and monitoring the response to antipsychotic therapy [34].

Regarding the apoptotic hypothesis of schizophrenia, it was proven that the mechanisms of G-protein signal transduction play a critical role in the regulation of programmed cell death, and experiments in vitro showed that the activation of G proteins can lead to neuronal apoptosis in cell line cultures [35]. According to the data of numerous postmortem studies, an imbalance of regulatory proteins of apoptosis was found in various parts of the brain of patients with schizophrenia [31]. The described data indicate a possible relationship between G proteins and schizophrenia, and also that genes encoding G proteins may be involved in the development of schizophrenia. Gene *GNAS*, encoding ubiquitously expressed Gαs, is of great interest as a candidate gene for schizophrenia for a number of reasons. First, the Gαs subunit plays a key role in the binding of dopamine D1/D5 receptors to adenylate cyclase [36]. In this regard, transgenic mice expressing the active form of Gαs represent an ideal model for certain schizophrenia endophenotypes [37]. According to the hypothesis of apoptosis in schizophrenia, it was found that increased expression of Gαs activates the signal transduction cascade of adenylcyclase, leading to the accumulation of the secondary intracellular messenger cAMP, which is the main player in proapoptotic processes [32].

There are a number of studies that have revealed increased expression of the Gαs protein in patients with bipolar disorder compared with the control, but which was lower in patients with unipolar depression [38]. This mechanism is based on a change in the level of neuronal apoptosis in the brain, dysregulation of the activity of the dopamine receptor D1 (DRD1) [36, 37], influence on the hypothalamic-pituitary axis [39], and dysregulation of the cAMP signaling pathway [40].

Gene *GNAS* encodes the neuroendocrine protein NESP55, expressed from the maternal allele [41]. NESP55 is highly expressed in a number of brain structures, including the hypothalamus, and in serotonergic neurons in the dorsal raphe nucleus, as well as in the locus coeruleus [41]. The NESP55 protein is known to be a specific serotonin 5HT1B receptor antagonist [42]. NESP55 knockout mice (with reduced expression from the maternal allele) showed normal growth parameters, hyperactivity, and abnormally high avoidance of new environments [41].

Thus, in the course of the described experiments on mouse models, two endophenotypes characteristic of autism spectrum disorders were presented: novelty aversion, which is the main feature of these disorders, and hyperactivity, which is especially common in autism, especially in early childhood [43]. However, differences in human and mouse cognition and behavior severely limit the strength of such conclusions. It is known that the gene *GNAS* also interacts with the gene *FMR1*, which is causal for autism spectrum disorder of fragile X syndrome [44].

Some mutations and epigenetic disorders in the gene *GNAS* lead to metabolic disorders in the thyroid gland [45, 46], including hypothyroidism due to changes in the expression of the *GNAS* transcript in the thyroid gland [46]. Hypothyroidism, and hyperparathyroidism, pseudohypoparathyroidism, and pseudopseudohypoparathyroidism are causally linked to several forms of psychosis, including Capgras syndrome (double denial delusions) and misidentification delusions that are typically characteristic of paranoid schizophrenia [47]. However, while psychosis is a relatively common feature of hypothyroidism, it is uncommon in the other two major diseases associated with dysregulation of gene *GNAS* (McCune-Albright syndrome and Albright's hereditary osteodystrophy). Thus, the nature of functional relationships between the level of expression of transcripts of gene *GNAS*, thyroid disease, and psychosis requires further study [48].

Chinese scientists have shown that altered imprinting of *GNAS* owing to folic acid deficiency contributes to intrauterine growth retardation and can lead to the development of a neural tube defect [49]. Hypermethylation of promoter *GNAS* in the basolateral amygdala regulates memory reconsolidation of the opioid reward system in rats [50]. A group of Korean researchers found an association of small genomic deletions in the gene *GNAS* with the risk of developing

Parkinson's disease [51]. The frequency of allele *rs587778384*T* in different populations was 0.1% (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs587778384).

The analysis of the frequency distribution of genotypes and alleles of the polymorphic locus rs587778384 of the gene *GNAS* showed that the genotype *rs587778384*C/C* occurred in patients with PS with a higher frequency (99.38%) than in the control group (94.0%) (p = 2.0E-09; OR = 10.31, CI95% = 4.12–25.81). Upon introducing the FDR correction (False Discovery Rate), the significance level p remained statistically significant (p_{fdr} = 1.82E-04) (Table 2). Heterozygous genotype *rs587778384*T/C*, on the contrary, is more common in the control group—in 6.00% of cases, compared with 0.62% in patients. The odds ratio score for genotype *rs587778384*T/C* was 0.1 (CI95% = 0.04–0.25, p = 2.0E-09; p_{fdr} = 2.82E-04) (Fig. 1, Table 2). The frequency of homozygous genotype *rs587778384*T/T* was 0.00% in both patients and healthy people.

Allele *rs587778384*C*, found with a frequency of 99.69 in patients and 97.0% in healthy individuals, is, accordingly, a marker of an increased risk of developing this disease (p = 6.13E-07; p_{fdr} = 0.017; OR = 10.02, CI95% = 4.01–25.03), and the allele *rs587778384*C* is a marker of a reduced risk of developing PS (p = 6.13E-07; p_{fdr} = 0.017; OR = 0.1, CI95% = 0.04–0.25).

Analysis of the association of the polymorphic variant rs587778384 of gene *GNAS* localized in the region 20q13.31 in different ethnic groups showed the existence of the most pronounced differences in the distribution of frequencies of alleles of SNP rs587778384 between the compared groups of patients and controls in Tatars (Table 2). Allele *rs587778384*C* in patients of Tatar ethnicity with PS were significantly more common (99.86%) than in the control group (97.1%) (p = 2.64E-03; OR = 21.19, CI95% = 2.85–157.63). The frequency of allele *rs587778384*T* in patients (0.14%) was higher than in healthy Tatars (2.9%) (p = 2.64E-03; OR = 0.05, CI95% = 0.01–0.37). However, after the introduction of the FDR correction, the differences were not statistically significant (p_{fdr} = 0.945) (Table 2). The prevalence of allele *rs587778384*C* in Russian patients with PS was higher (100.0%) than in healthy Russians (96.73%) (p = 8.1E-03; p_{fdr} = 1.354; OR = 43.9, CI95% = 5.95–323.97). The frequency of allele *rs587778384*T* in patients was 0.00% and in healthy people was 3.27% (p = 8.1E-03; p_{fdr} = 1.354; OR = 0.02, CI95% = 0–0.15). Allele *rs587778384*C* in Bashkir patients with PS was more common (98.55%) than in the control group (97.29%), but the differences were not statistically significant (p = 0.273; p_{fdr} = 0.968) (Table 2).

Published data on the study of the association of SNP rs587778384 with paranoid schizophrenia, mental illness, and other multifactorial diseases were not found. However, to date, there are a number of studies that have studied the association of polymorphic loci located in the 20q13.31 region with schizophrenia and other mental illnesses in various populations.

It is known that the polymorphic locus C393T of the gene *GNAS*, representing a synonymous substitution, can affect the expression of Gαs. Individuals with the genotype *C393T*T/T* have increased expression of Gαs, as well as a greater vulnerability to apoptosis in various cell types [52]. In this regard, R. Minoretti et al. hypothesized that the genotype *C393T*T/T* of gene *GNAS* may confer an increased predisposition to the development of schizophrenia. As a result of the study, these authors revealed the association of the genotype *C393T*T/T* (*rs7121*) with negative symptoms in Italian patients with schizophrenia [33]. In a GWAS study, L. Athanasiu et al. showed that the polymorphic locus rs6100223, located at a distance of 58 kb from the gene *GNAS*, was associated with schizophrenia with a fairly high level of significance (p = 5.95E-04) among the Norwegians [53].

In a genome-wide association study of 2454 European schizophrenic patients with positive, negative, and general psychopathological symptoms, no SNPs reached the genome-wide significance level of 1.67E-08. However, a number of genes and chromosomal regions (among which there was a polymorphic locus located in the chromosomal region 20q13.31) were identified that are associated with schizophrenia with a high level of significance, both with positive symptoms (rs11699237, p = 9.96E-06) and negative symptoms (rs11699237 p = 3.13E-06) [54].

It is known that brain oscillations are characteristic features of active neural networks; with a certain frequency, rhythms correlate with sensory perception and cognitive activity, including in consciousness, memory, and stimulus processing. As a result of a genome-wide study in 771 patients of European and 293 African-American origin, an association of polymorphic loci rs13831 (p = 6.04E-05) and rs6026576 (p = 7.79E-06) of gene *GNAS* was shown with this endophenotype in patients with alcoholism [55].

R. Minoretti et al. found an association of genotype *C393T*T/T* of gene *GNAS* with increased expression of the Gαs protein and the risk of developing schizophrenia with negative symptoms. These results, as well as those obtained in experiments on mice [33], suggest that a high level of expression of the imprinted gene from the maternal allele is associated with schizophrenia [48]. It was found that differential methylation in imprinting genes, including gene *GNAS*, indicates that neurodevelopmental disorders underlie the 22q11.2DS deletion syndrome in schizophrenia [56]. According to a number of genome-wide studies, linkage of the chromosomal region 20q13 with bipolar disorder in individuals of Middle Eastern (Israel) and European origin is known [57, 58]. Thus, in this study, for the first time, an association of single nucleotide polymorphic

variants was established—rs73254185 (localized in the 4p15.2 region) and rs587778384 of gene *GNAS* (20q13.31)—with the development of paranoid schizophrenia in individuals of different ethnicity, Russians, Tatars, and Bashkirs living in the Republic of Bashkortostan, which may indicate the involvement of genes *PI4K2B* and *GNAS* localized in these chromosomal regions in the pathogenesis of schizophrenia. However, replication studies are needed to confirm the results obtained.

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COMPLIANCE WITH ETHICAL STANDARDS

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

Statement of compliance with standards of research involving humans as subjects. All procedures performed with participation of people 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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