ISSN 1022-7954, Russian Journal of Genetics, 2024, Vol. 60, No. 1, pp. 132–136. © Pleiades Publishing, Inc., 2024.

SHORT COMMUNICATIONS

Novel Genetic Risk Marker for Paranoid Schizophrenia in the Chromosomal Region 9q21.13 in Tatars: A Genome-Wide Association Analysis

A. E. Gareeva[a, b, *]

[a] *Institute of Biochemistry and Genetics, Ufa Federal Research Center, Russian Academy of Sciences, Ufa, 450054 Russia*

[b] *Bashkir State Medical University, Ufa, 450008 Russia*

**e-mail: annagareeva@yandex.ru*

Received June 6, 2023; revised July 5, 2023; accepted July 11, 2023

Abstract—Schizophrenia, the most common severe mental illness, leads to a serious decrease in higher functions, mainly to a change in cognitive functions and perception of reality. Both genetic and environmental factors are involved in its pathogenesis; however, its genetic component still needs to be studied. The aim of the study was to identify genetic markers of paranoid schizophrenia in Tatars from the Republic of Bashkortostan. Genome-wide genotyping of DNA samples was carried out on the PsychChip biochip, which included 610000 single nucleotide polymorphic variants (SNPs). The studied sample consisted of 357 patients with paranoid schizophrenia and 383 healthy individuals of Tatar ethnicity. As a result of the study, the association of the SNP rs12376586 of the *MAMDC2* gene located in the region 9q21.13 with the development of paranoid schizophrenia in Tatars living in the Republic of Bashkortostan was established for the first time.

Keywords: genetics, schizophrenia, genome-wide association analysis, ethnicity, ethnospecific markers, Republic of Bashkortostan, Psychiatric Genomics Consortium (PGC)

DOI: 10.1134/S1022795424010071

Schizophrenia is a severe and chronic mental disorder with a lifetime prevalence of approximately 1%. The disease is characterized by delusions, hallucinations, lack of motivation, alogia, and cognitive impairment [1]. Twin studies have shown that the heritability rate for schizophrenia is approximately 79–81% [1].

Genome-wide association studies (GWAS) have led to significant advances in identifying polymorphic risk loci and analyzing the genetic architecture of schizophrenia [1]. For example, the Psychiatric Genomics Consortium (PGC) and other research groups have conducted large-scale GWAS studies over the past decade and identified many single nucleotide polymorphic variants (SNPs) associated with schizophrenia [2–5]. In addition, M. Lam et al. conducted a meta-analysis involving 56418 patients with schizophrenia and 78818 healthy individuals, combining the results of studies in European and East Asian populations, and identified 176 genetic risk markers for schizophrenia [4].

In order to identify ethnospecific genetic risk factors for the development of paranoid schizophrenia, we conducted a genome-wide association analysis in Tatars from the Republic of Bashkortostan. The object of the study is 357 patients (184 men, 173 women) of Tatar ethnicity diagnosed with paranoid schizophrenia (PS) F20.xx according to the international classification of diseases, 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 average age of the patients was 24.9 ± 8.9 years. The average age of onset of the disease was 22.4 ± 7.3 years. Information on ethnicity up to the third generation was obtained by interview. The control group consisted of 383 healthy individuals of the same age group who were not registered with a psychiatrist or narcologist and denied a family history of mental illness. The average age of healthy donors was 32.4 ± 12.4 years.

Whole-genome genotyping of DNA samples was carried out on an Illumina Human 610-QuadPsychChip biochip, which included 610000 SNPs. GWAS analysis of these polymorphic variants was performed using the PLINK 2.0 software package [6]. A detailed description of the genome-wide association analysis was published previously [7]. To reduce the error of the first type, the FDR-BH correction (False Discovery Rate Bengamini–Hochberg) was applied to the number of multiple comparisons [8].

A genome-wide association analysis performed in individuals of Tatar ethnicity revealed the most pronounced differences between patients with PS and the

Table 1. Single nucleotide polymorphic variants localized in the 9q21.12 region and associated with paranoid schizophrenia in Tatars

Gene	rs no.	SNP	Allele 1	Frequency of allele 1, patients, %	Frequency of allele 1, control, %	Allele 2	p	p_{fdr}	OR
–	rs12376586	g.72648582A>G	*G*	0.359	0.496	*A*	1.89E-07	0.005	0.569
–	rs11141100	g.72591525A>G	*G*	0.350	0.469	*A*	6.72E-06	0.158	0.6178
–	rs4446788	g.72637119C>A	*C*	0.519	0.424	*A*	0.000238	0.909	1.482
–	rs1565691	g.72609532T>C	*T*	0.461	0.368	*C*	3.75E-04	0.925	1.459
–	rs7032845	g.72562231G>A	*A*	0.379	0.465	*G*	1.18E-03	0.925	0.711
MAMDC2	rs4744982	g.72749590G>A	*G*	0.221	0.157	*A*	1.56E-03	0.925	1.545
MAMDC2	rs10780851	g.72766144C>T	*C*	0.254	0.189	*T*	2.21E-03	0.925	1.489
–	rs10868358	g.72611680G>T	*G*	0.251	0.187	*T*	2.79E-03	0.932	1.47
–	rs10511975	g.72530831T>G	*G*	0.296	0.372	*T*	2.91E-03	0.932	0.722
–	rs11141106	g.72593325T>G	*G*	0.311	0.243	*T*	3.75E-03	0.932	1.404
MAMDC2	rs1927103	g.72722865G>A	*G*	0.43	0.359	*A*	6.14E-03	0.932	1.336
MAMDC2	rs10511980	g.72738339A>G	*A*	0.406	0.338	*G*	7.17E-03	0.932	1.338
MAMDC2	rs4744977	g.72728822G>A	*G*	0.364	0.302	*A*	0.011	0.932	1.331
MAMDC2	rs10511981	g.72739478C>T	*C*	0.0854	0.0548	*T*	0.024	0.954	1.592

control group in polymorphic loci located in the 9q21.12 region (Fig. 1). The highest association of PS is observed with SNP rs12376586 (p = 1.89E-07) (Table 1).

According to the 1000 Genomes Project, the frequency of allele *rs12376586*G* in populations of the world varies from 6.8% in the Chinese (CHB) populations, 9% in the African (AFR) populations, and up to 55% in the populations of European origin (CEU) (https://www.ensembl.org/Homo_sapiens/Variation/Population?db=core;v=rs12376586;vdb=variation).

The closest gene, located at a distance of about 10 kb from this polymorphic locus, is the gene *MAMDC2*. The chromosomal region 9q21.12, in which the gene *MAMDC2* is located, is associated with a rare congenital disease manifested by characteristic facial features and mental retardation—Kabuki syndrome in the Japanese [9]. Gene *MAMDC2* encodes the MAM protein containing domain 2 (mephrin, A5 antigen, protein tyrosine phosphatase mu). It is known that this protein is involved in glycosaminoglycan metabolism. Gene *MAMDC2* consists of 14 exons, covering about 183 kb of genomic DNA; currently, 1182 SNPs have been identified in this gene. Disorders of glycosaminoglycan metabolism lead to the development of a whole class of diseases—mucopolysaccharidosis. To date, at least 11 disorders of mucopolysaccharide metabolism with different primary biochemical defects are known, i.e., deficiency of various enzymes. The entire group is united by increased accumulation of acidic mucopolysaccharides in cells and increased excretion of these substances in the urine. Most of these diseases are characterized by changes in the skeleton and internal organs, expressed in different forms to varying degrees, and are accompanied by severe disorders of the nervous system leading to severe dementia [10].

In experimental animal models of Alzheimer's disease, it was found that the gene *MAMDC2*, highly expressed in microglia, positively regulates the innate antiviral response to neurotropic viral infection [11]. Additionally, exome sequencing revealed mutations *de novo* in 32 genes, including *MAMDC2*, associated with mental retardation [12]. Scientists from Turkey identified an association of the chromosomal region 9q21.12-21.31 with a neural tube defect, namely, meningomyelocele [13].

In the sample of patients and controls of Tatar ethnicity that we studied, the highest level of association of paranoid schizophrenia was found with SNP rs12376586. Homozygous genotype *rs12376586*G/G* in the patients with paranoid schizophrenia was rare, in 13.17% of cases, and in the controls, it was detected more often—in 24.54% of cases (p = 8.02E-05, OR = 0.47, CI95% 0.31–0.70). The frequency of genotype *rs12376586*A/A* was significantly higher in patients with PS than in the control group of individuals (41.46 and 25.33%, respectively) (p = 3.2E-06, OR = 2.09, CI95% 1.51–2.89).

Correction for multiple comparisons FDR showed no statistically significant differences (*rs12376586*G/G* p_{fdr} = 0.999, *rs12376586*G/A* p_{fdr} = 0.881, *rs12376586*A/A* p_{fdr} = 0.451) (Table 2).

Analysis of the allele frequency distribution of this polymorphic locus showed that the frequency of allele *rs12376586*G* in the patients with PS was lower (35.85%) than in the controls (49.61%). Allele

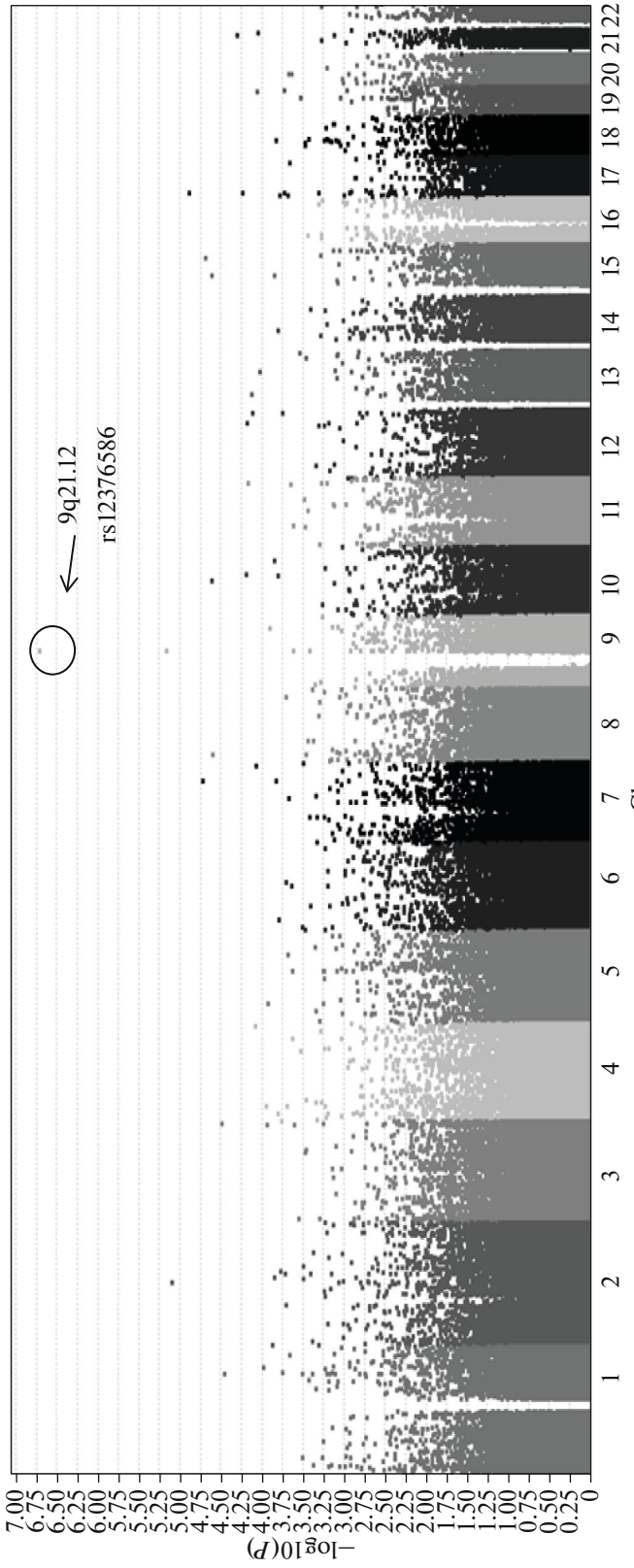

Fig. 1. Graphic representation of the results of a genome-wide analysis of the association of 395832 SNPs with paranoid schizophrenia in Tatars (Manhattan plot). The *x* axis shows the chromosomal localization of SNPs; the *y* axis shows the values of the negative decimal logarithm of the *p*-value significance level.

Table 2. Distribution of frequencies of genotypes and alleles of the rs12376586 polymorphic variant in samples of patients with paranoid schizophrenia and in control groups in Tatars

Genotype, allele	Patients		Control		p	p_{fdr}	OR (CI95%)
	n_i	$p_i \pm S_p$ CI, %	n_i	$p_i \pm S_p$ CI, %			
rs12376586							
G/G	47	13.17 ± 1.79 9.84–17.12	94	24.54 ± 2.2 20.31–29.17	8.2E-05	0.999	0.47 (0.31–0.70)
G/A	162	45.38 ± 2.63 40.13–50.7	192	50.13 ± 2.55 45.01–55.25	0.196	0.881	–
A/A	148	41.46 ± 2.61 36.3–46.76	97	25.33 ± 2.22 21.05–29.99	3.2E-06	0.451	2.09 (1.51–2.89)
G	256	35.85 ± 1.79 32.33–39.49	380	49.61 ± 1.81 46.01–53.21	1.89E-07	0.05	0.57 (0.46–0.7)
A	458	64.15 ± 1.79 60.51–67.67	386	50.39 ± 1.81 46.79–53.99	1.89E-07	0.05	1.76 (1.43–2.17)
rs11141100							
G/G	45	12.61 ± 1.76 9.34–16.5	87	22.72 ± 2.14 18.61–27.24	3.3E-04	0.999	0.49 (0.32–0.74)
G/A	160	44.82 ± 2.63 39.58–50.14	185	48.3 ± 2.55 43.2–53.43	0.342	0.936	–
A/A	152	42.58 ± 2.62 37.39–47.89	111	28.98 ± 2.32 24.49–33.81	1.1E-04	0.999	1.82 (1.32–2.49)
G	250	35.01 ± 1.79 31.51–38.64	359	46.87 ± 1.8 43.29–50.47	6.72E-06	0.632	0.61 (0.49–0.75)
A	464	64.99 ± 1.79 61.36–68.49	407	53.13 ± 1.8 49.53–56.71	6.72E-06	0.632	1.64 (1.33–2.02)

*rs12376586*A* in the patients with PS was determined in 64.15 of cases, and in the healthy people, it was in 50.39%. The odds ratio for allele *rs12376586*G* was 0.57 (CI95% 0.46–0.7) (p = 1.89E-07), for allele *rs12376586*A*, it was 1.76 (CI95% 1.43–2.17). When introducing the FDR correction, the significance level remained statistically significant (*rs12376586*G* p_{fdr} = 0.05, *rs12376586*A* p_{fdr} = 0.05) (Table 2).

The polymorphic single-nucleotide variant rs11141100 in the sample of patients and controls of Tatar ethnicity that we studied showed a high level of association with PS (p = 6.72E-06) (Table 1).

In patients with paranoid schizophrenia, the frequency of the homozygous genotype *rs11141100*G/G* (12.61%) was significantly lower than that in the control group (22.72%) (p = 3.3E-04, OR = 0.49, CI95% 0.32–0.74). Genotype *rs11141100*A/A* was more common in patients with PS (42.58%) than in the control group of individuals (28.98%) (p = 1.1E-04, OR = 1.82, CI95% 1.32–2.49). The frequency of allele *rs11141100*G* in the group of healthy individuals was significantly higher (46.87%) than in the patients with PS (35.01%) (p = 6.72E-05, OR = 0.61, CI95% 0.49–0.75). The frequency of allele *rs11141100*A* in the patients with PS (64.99%) exceeded its frequency in the control group, where it was 53.13% (OR = 1.64, CI95% 1.33–2.02). However, after introducing the FDR correction, the significance level turned out to be statistically insignificant (*rs11141100*G/G* p_{fdr} = 0.999, *rs11141100*G/A* p_{fdr} = 0.936, *rs11141100*A/A* p_{fdr} = 0.999, *rs11141100*G* p_{fdr} = 0.632, *rs11141100*A* p_{fdr} = 0.632) (Table 2).

Thus, in our genome-wide study, the association of the single nucleotide polymorphic variant rs12376586 of the gene *MAMDC2* was established for the first time, located in the region 9q21.13, with the development of paranoid schizophrenia in Tatars. The genetic marker of the risk of developing paranoid schizophrenia in individuals of Tatar ethnicity is the allele *rs12376586*A*. The genetic marker of a reduced risk of developing PS in individuals of Tatar ethnicity is the allele *rs12376586*G*.

Previously, according to the literature, the association of paranoid schizophrenia with this region and gene *MAMDC2* was not detected in any population. The results of studies on its expression and polymor-

phic variants are very limited. However, given the data on the participation of the protein encoded by the gene *MAMDC2* in the metabolism of glycosaminoglycans, it can be assumed that polymorphic variants of this gene can play an important role in the formation of the structure of hereditary predisposition to paranoid schizophrenia in Tatars.

ACKNOWLEDGMENTS

The author expresses her deep gratitude to the staff of the Department of Psychiatric Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK, M. O'Donovan, V. Escott-Price, M. Owen, and G. Leonenko for advice on data generation and analysis and participation in the project. Special thanks go to Prof. E.K. Khusnutdinova, director of the Institute of Biochemistry and Genetics, Ufa Federal Research Center, Russian Academy of Sciences, for scientific advice.

FUNDING

This work was supported by ongoing institutional funding. No additional grants to carry out or direct this particular research were obtained.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed voluntary consent was obtained from each of the participants included in the study. The study was approved by the Ethics Committee of the Institute of Biochemistry and Genetics-Subdivision of the Ufa Federal Research Centre of the Russian Academy of Sciences, protocol No. 4 dated March 27, 2009. All participants were adults.

CONFLICT OF INTEREST

The author of this work declares that she has no conflicts of interest.

REFERENCES

1. Li, S., Li, J., Liu, J., et al., Regulatory variants at 2q33.1 confer schizophrenia risk by modulating distal gene TYW5 expression, *Brain*, 2022, vol. 145, no. 2, pp. 770–786. https://doi.org/10.1093/brain/awab357
2. Trubetskoy, V., Pardiñas, A.F., Qi, T., et al., Mapping genomic loci implicates genes and synaptic biology in schizophrenia, *Nature*, 2022, vol. 604, no. 7906, pp. 502–508. https://doi.org/10.1038/s41586-022-04434-5
3. Ikeda, M., Takahashi, A., Kamatani, Y., et al., Genome-wide association study detected novel susceptibility genes for schizophrenia and shared trans-populations/diseases genetic effect, *Schizophr. Bull.*, 2019, vol. 45, no. 4, pp. 824–834. https://doi.org/10.1093/schbul/sby140
4. Lam, M., Chen, C.Y., Li, Z., et al., Comparative genetic architectures of schizophrenia in East Asian and European populations, *Nat. Genet.*, 2019, vol. 51, no. 12, pp. 1670–1678. https://doi.org/10.1038/s41588-019-0512-x
5. Pardiñas, A.F., Holmans, P., Pocklington, A.J., et al., Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection, *Nat. Genet.*, 2018, vol. 50, no. 3, pp. 381–389. https://doi.org/10.1038/s41588-018-0059-2
6. Purcell, S., Neale, B., Todd-Brown, K., et al., PLINK: a toolset for whole-genome association and population-based linkage analysis, *Am. J. Hum. Genet.*, 2007, vol. 81, no. 3, pp. 559–575. https://doi.org/10.1086/519795
7. Gareeva, A.E., Genome-wide association study of the risk of schizophrenia in the Republic of Bashkortostan, *Russ. J. Genet.*, 2023, vol. 59, no. 8, pp. 831–839. https://doi.org/10.1134/S1022795423080070
8. Benjamini, Y., Drai, D., Elmer, G., et al., Controlling the false discovery rate in behavior genetics research, *Behav. Brain Res.*, 2001, vol. 125, nos. 1–2, pp. 279–284. https://doi.org/10.1016/s0166-4328(01)00297-2
9. Kuniba, H., Yoshiura, K., Kondoh, T., et al., Molecular karyotyping in 17 patients and mutation screening in 41 patients with Kabuki syndrome, *J. Hum. Genet.*, 2009, vol. 54, no. 5, pp. 304–309. https://doi.org/10.1038/jhg.2009.30
10. Carvalho, S., Santos, J.I., Moreira, L., et al., Neurological disease modeling using pluripotent and multipotent stem cells: a key step towards understanding and treating mucopolysaccharidoses, *Biomedicine*, 2023, vol. 11, no. 4. https://doi.org/10.3390/biomedicines11041234
11. Wang, Y., Luo, W., Wang, X., et al., *MAMDC2*, a gene highly expressed in microglia in experimental models of Alzheimer's disease, positively regulates the innate antiviral response during neurotropic virus infection, *J. Infect.*, 2022, vol. 84, no. 2, pp. 187–204. https://doi.org/10.1016/j.jinf.2021.12.004
12. Anazi, S., Maddirevula, S., Faqeih, E., et al., Clinical genomics expands the morbid genome of intellectual disability and offers a high diagnostic yield, *Mol. Psychiatry*, 2017, vol. 22, no. 4, pp. 615–624. https://doi.org/10.1038/mp.2016.113
13. Bayri, Y., Soylemez, B., Seker, A., et al., Neural tube defect family with recessive trait linked to chromosome 9q21.12-21.31, *Childs Nerv. Syst.*, 2015, vol. 31, no. 8, pp. 1367–1370. https://doi.org/10.1007/s00381-015-2753-z

Publisher's Note. Pleiades Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.