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HUMAN GENETICS

Association Study of Genetic Markers of Schizophrenia and Its Cognitive Endophenotypes

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Abstract—A replicative analysis of associations of 15 SNPs located in the regions of 11 genes (*TCF4*, *VRK2*, *NOTCH4*, *ZNF804A*, *AGBL1*, *RELN*, *ZFP64P1*, *KCNB2*, *CSMD1*, *CPVL*, *NRIP1*) and three intergenic regions (*SLCO6A1/LINCOO491, LOC105376248/LOC105376249, SPA17/NRGN*) with schizophrenia was conducted in the Russian population of the Siberian region. These SNPs were previously identified in genome-wide association studies (GWAS) of schizophrenia and cognitive abnormalities. The present study confirmed associations of *KCNB2* rs2247572, *CSMD1* rs2616984, and intergenic rs12807809 located in *SPA17/NRGN* with schizophrenia. It was established that the frequency of the *CSMD1* rs2616984 *G/G* genotype was higher in patients compared to the control group (OR = 1.73; CI: 1.14–2.62; $p = 0.0337$). The frequencies of the *KCNB2* rs2247572 *TT* genotype (OR = 0.41; CI: 0.20–0.87; $p = 0.0485$) and intergenic rs12807809 *CT* genotype located in *SPA17/NRGN* (OR = 0.70; CI: 0.53–0.94; $p = 0.0464$) were significantly decreased in patients compared to the control group.

Keywords: schizophrenia, cognitive endophenotypes, association study, multifactorial diseases, Russian population

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INTRODUCTION

In recent decades, schizophrenia became one of the most studied diseases in both Russian and foreign studies. According to the National Center for Biotechnology Information (NCBI), the number of studies exploring this disease increases every year [1]. One of the reasons includes worldwide distribution of schizophrenia, which is estimated at 0.8–1% [2]. The World Health Organization in 2001 placed this disorder on the list of ten reasons resulting in disabilities at a young age (15–44 years) [3]. Compared to other psychiatric disorders accompanied by cognitive disabilities, schizophrenia occurs in individuals at their social prosperity and reproductive age.

Undoubtedly, schizophrenia is a heterogenic disease in both etiology and clinical manifestation. The disease development is caused by a combination of various factors in different individuals, and its clinical manifestation also varies. However, the elements relatively constant during the disease development, which might reflect the total dysfunction in the brain, are known. Impaired cognitive processes related to prefrontal cortex functioning represent such elements. Moreover, cognitive functions are affected unevenly; for instance, executive functions, social cognition, and working and verbal memory are affected to a major extent, while attention and memory are less affected [3]. Cognitive disabilities represent an important and relatively independent component of schizophrenic symptoms.

To date, no worldwide accepted concept of etiology and pathogenesis of schizophrenia exists. However, the multifactorial nature of schizophrenia with polygenic type of inheritance is undoubted. This was reported by multiple and diverse studies (twin, clinical-genetic, and epidemiological). According to foreign studies, the relative impact of the genetic factor in schizophrenia etiology and pathogenesis is 60–70%, while the remaining 30–40% belongs to environmental factors [4].

From the middle of the 20th century, the role of the genetic factor in schizophrenia was explored in candidate gene association studies. This approach made it possible to detect the prospective genes involved in developing schizophrenia. Recently, genome-wide association studies (GWAS) became the novel approach to determine the genes having susceptibility to multifactorial disorders. Such studies based on

simultaneous association analysis of multiple SNPs with a disease made it possible to detect hundreds of thousands of SNPs possibly associated with this disorder. For instance, genotyping of SNPs on DNA as micromatrices in the genome-wide association studies of schizophrenia resulted in detection of genetic loci with a small effect (OR 1.1–1.5), which in summary might explain about 25% of variation in genetic predisposition to schizophrenia [5]. According to the GWAS database [6], 74 genome-wide association studies of schizophrenia have been performed in samples consisting of several thousand patients and healthy individuals. The majority of these studies were carried out in Caucasoids from Europe and North America, while the structure of genetic variability of this disorder in other geographic regions, including Russia, remains unknown. Moreover, 27 GWAS of potential endophenotypes of schizophrenia such as cognitive traits and functions were performed [6].

Replicative studies of SNPs determined in GWAS need to be conducted in independent samples differing in ethnicity in order to confirm statistically significant associations with phenotypes and to reveal ethnic specificity of these relations.

Several research groups have been actively exploring the pathophysiology of schizophrenia, disease association with candidate genes, and ethnic specificity of this disease in Russia [7–11].

The present study was aimed at conducting replicative association analysis of 15 polymorphisms previously detected in GWAS of schizophrenia and its cognitive endophenotypes with schizophrenia in the Russian population of the Siberian region.

MATERIALS AND METHODS

The case group consisted of patients from the Research Institute of Medical Genetics (Tomsk, Russia). All patients were subjected to standard neuropsychological tests, and nosology of psychiatric and behavioral disorders was based on ICD-10 diagnostical criteria (*F20*) performed by researchers from the Research Institute of Medical Genetics (Tomsk, Russia). The group of patients consisted of 389 Russian individuals from the Siberian region, including 241 men (61.95%) and 148 women (38.05%). The mean age of patients was 39.7 (±13.3) years; the youngest individual was 18 years old, and the oldest was 70 years old. The mean age of schizophrenia manifestation was 25.3 (±8.9) years and the mean disease duration was 14.4 (±11.2) years.

The control group consisted of 674 unrelated individuals from the Russian population: 377 men (55.93%) and 297 women (44.07%) without psychiatric and neurological diseases in anamnesis. The mean age in the control group was 34.7 (±14.0) years; the youngest individual was 18 years old, and the oldest was 69 years old. This study was approved by the bioethics committee of the Research Institute of Medical Genetics (Tomsk, Russia). Informed consent was obtained from each individual during the collection of material.

Fifteen SNPs located in the regions of genes (*TCF4*, *VRK2*, *NOTCH4*, *ZNF804A*, *AGBL1*, *RELN*, *ZFP64P1*, *KCNB2*, *CSMD1*, *CPVL*, *NRIP1*) and intergenic regions (*SLCO6A1/LINCOO491*, *LOC105376248/LOC105376249*, *SPA17/NRGN*) were studied in the present study. They were selected on the basis of the following criteria:

(1) high level of significance of association with phenotype (schizophrenia or cognitive traits assumed to be schizophrenia endophenotypes such as working memory, episodic memory, attention control, and speech) determined in GWAS ($p \leq 5 \times 10^{-6}$) [4, 12–17];

(2) single nucleotide polymorphism (SNP);

(3) minor allele frequency >5% in at least one HapMap population;

(4) confirmed gene/SNP effect in several replication studies or in meta-analysis.

The characteristics of 15 explored SNPs are shown in Table 1.

DNA was extracted via the standard phenol-chloroform technique from the peripheral venous blood leukocytes. Genotyping was carried out via real-time PCR using TaqMan probes (Applied Biosystems, United States) according to the manufacturer's recommendations in the real-time PCR detection system (Bio-Rad, United States).

Statistical analysis was performed via Statistica 7.0. The correspondence of the distribution of genotype frequencies of the studied SNPs to that expected by the Hardy–Weinberg equilibrium was tested via Fisher's exact test [18]. Pairwise comparison of allele and genotype frequencies between analyzed groups was conducted via Pearson's chi-square test with Yates' correction for continuity. The odds ratio (OR) was calculated to estimate SNPs association with pathologic phenotype. Differences were considered statistically significant for $p < 0.05$.

RESULTS

The distribution of allele and genotype frequencies of studied SNPs and the chi-square test with Yates' correction for continuity and significance level for this test obtained as a result of comparison of allele and genotype frequencies between schizophrenic patients and control group are shown in Table 2. The frequency of a derivative ("mutant") allele varied from 1.5 to 93.56% depending on SNP.

The distribution of frequencies of alleles and genotypes in the majority of explored SNPs in the tested groups corresponded to Hardy–Weinberg equilibrium except for *CSMD1* rs2616984 and intergenic

Table 1. Characteristics of the studied SNPs

No.	Intergenic region, gene (location)	SNP ID	Alleles	SNP location	Association in GWAS (reference)
1	*SLCO6A1 /LINC00491* (5q21.1)	rs1502844	*C/T**	Intergenic region	Schizophrenia [4]
2	*TCF4* (18q21.2)	rs9960767	*A*/C*	Intron	Schizophrenia [4]
3	*VRK2* (2p16.1)	rs2312147	*C*/T*	Intron	Schizophrenia [4]
4	*NOTCH4* (6p21.32)	rs3131296	*C*/T*	Intron	Schizophrenia [4]
5	*LOC105376248/LOC105376249* (9q33.1)	rs1572299	*C/T**	Intergenic region	Schizophrenia [4]
6	*TCF4* (18q21.2)	rs17594526	*C*/T*	Intron	Schizophrenia [12]
7	*ZNF804A* (2q32.1)	rs1344706	*C/A**	Intron	Schizophrenia [16]
8	*AGBL1* (15q25.3)	rs16977195	*A*/G*	Intron	Schizophrenia [17]
9	*RELN* (7q22.1)	rs7341475	*A/G**	Intron	Schizophrenia [13]
10	*ZFP64P1* (14q22.1)	rs8020441	*G*/T*	Pseudogene	Cognitive ability [14]
11	*KCNB2* (8q13.3)	rs2247572	*C*/T*	Intron	Cognitive ability [14]
12	*CSMD1* (8p23.2)	rs2616984	*A*/G*	Intron	Cognitive ability [14]
13	*CPVL* (7p14.3)	rs2252521	*C/T**	Intron	Cognitive ability [15]
14	*SPA17/NRGN* (11q24.2)	rs12807809	*C*/T*	Intergenic region	Schizophrenia [4]
15	*NRIP1* (21q11.2)	rs2229741	*C*/T*	Intron	Cognitive ability [15]

* Marks ancestral allele.

SPA17/NRGN rs12807809 in patients, as well as *VRK2* rs2312147, *AGBL1* rs16977195, and *KCNB2* rs2247572 in the control group.

Statistically significant differences in genotype frequencies of *CSMD1* rs2616984 between schizophrenic patients and control group were detected (Table 2): the frequency of *G/G* genotype was significantly higher in patients compared to the control (OR = 1.73; CI: 1.14–2.62; $p = 0.0337$).

Two other SNPs (*KCNB2* rs2247572 and intergenic *SPA17/NRGN* rs12807809) demonstrated associations of allelic variants with schizophrenia resulting in a decreased risk of disease development. The frequency of *KCNB2* rs2247572 *T/T* genotype was significantly lower in patients compared to the control group (OR = 0.41; CI: 0.20–0.87; $p = 0.0485$). The frequency of *SPA17/NRGN* rs12807809 *C/T* genotype was significantly lower in patients than in the control group (OR = 0.70; CI: 0.53–0.94; $p = 0.0464$).

The comparison of allele frequencies and calculation of the odds ratio are demonstrated in Table 3. Statistically significant association of alleles was detected for the one of 15 SNPs. The frequency of a minor allele of *KCNB2* rs2247572 (OR = 0.79; CI: 0.62–1.00; $p = 0.0468$) was significantly lower in individuals with schizophrenia compared to the control group (Table 3). Three loci demonstrated a trend toward association with schizophrenia: *RELN* rs7341475 ($p = 0.0984$), *CSMD1* rs2616984 ($p = 0.0802$), and *CPVL* rs2252521 ($p = 0.0602$).

DISCUSSION

Recently, different publications reported the role of the *CSMD1* gene in liability to different neurological and psychiatric diseases, including Alzheimer's disease, bipolar disorder, and schizophrenia [19–22]. For instance, Koiliari et al. [23] demonstrated that rs10503253 located in this gene and previously associated with schizophrenia in GWAS significantly affected total cognitive ability and executive functions in healthy Europeans from Greece. The authors suggested that one of the alleles significantly unfavorably affects cognitive functions, which might represent the part of a mechanism resulting in increased risk of schizophrenia [23].

The *CSMD1* gene is expressed in all tissues, while the highest protein level is observed in the brain. The *CSMD1* gene encodes for transmembrane regulatory protein consisting of multiple SUB and Sushi domains involved in control of a complement cascade [24, 25]. The complement system represents a protein complex

Table 2. Distribution of genotype and derivative ("mutant") alleles of the studied SNPs in explored groups

No.	Polymorphism (intergenic region, gene), ($N_{case}/N_{control}$)	Genotype, allele	Frequency in case group (N_{case})	Frequency in control group ($N_{control}$)	Chi-square (significance level)
1	rs1502844 (*SLCO6A1/LINC00491*), (388/674)	*CC*	0.1572 (61)	0.1513 (102)	1.99 (0.1583)
		CT	0.4923 (191)	0.4421 (298)	
		TT	0.3505 (136)	0.4065 (274)	
		C	0.4034	0.3724	3.4 (0.1826)
2	rs9960767, (*TCF4)*, (389/673)	*AA*	0.9460 (368)	0.9212 (620)	2.33 (0.3119)
		AC	0.0540 (21)	0.0788 (53)	
		CC	0.0000 (0)	0.0000 (0)	
		C	0.0270	0.0394	2.25 (0.1336)
3	rs2312147 (*VRK2*), (387/671)	*CC*	0.3463 (134)	0.3756 (252)	4.11 (0.1280)
		CT	0.4884 (189)	0.4262 (286)	
		TT	0.1654 (64)	0.1982 (133)	
		C	0.5904	0.5887	0.01 (0.9203)
4	rs3131296 (*NOTCH4*), (389/674)	*CC*	0.8226 (320)	0.7923 (534)	2.31 (0.3150)
		CT	0.1697 (66)	0.1914 (129)	
		TT	0.0077 (3)	0.0163 (11)	
		C	0.9075	0.8880	1.99 (0.1583)
5	rs1572299 (*LOC105376248/LOC105376249*), (389/674)	*CC*	0.1825 (71)	0.1899 (128)	0.81 (0.6669)
		CT	0.4730 (184)	0.4926 (332)	
		TT	0.3445 (134)	0.3175 (214)	
		C	0.4190	0.4362	0.59 (0.4424)
6	rs17594526 (*TCF4)*, (389/668)	*CC*	0.9820 (382)	0.9701 (648)	1.41 (0.4941)
		CT	0.0180 (7)	0.0299 (20)	
		TT	0.0000 (0)	0.0000 (0)	
		T	0.0090	0.0150	1.39 (0.2384)
7	rs1344706 (*ZNF804A*), (388/673)	*AA*	0.4227 (164)	0.4279 (288)	0.45 (0.7985)
		AC	0.4304 (167)	0.4398 (296)	
		CC	0.1469 (57)	0.1322 (89)	
		A	0.6379	0.6478	0.21 (0.6467)
8	rs16977195 (*AGBL1*), (388/674)	*AA*	0.8789 (341)	0.8769 (591)	0.19 (0.9093)
		AG	0.1134 (44)	0.1128 (76)	
		GG	0.0077 (3)	0.0104 (7)	
		A	0.9356	0.9332	0.04 (0.8414)
9	rs7341475 (*RELN*), (389/673)	*AA*	0.0463 (18)	0.0253 (17)	3.91 (0.1415)
		AG	0.2828 (110)	0.2689 (181)	
		GG	0.6710 (261)	0.7058 (475)	
		G	0.8123	0.8403	2.73 (0.0984)

Table 2. (Contd.)

No.	Polymorphism (intergenic region, gene), ($N_{case}/N_{control}$)	Genotype, allele	Frequency in case group (N_{case})	Frequency in control group ($N_{control}$)	Chi-square (significance level)
10	rs8020441 (*ZFP64P1*), (388/674)	*GG*	0.0387 (15)	0.0415 (28)	
		GT	0.2990 (116)	0.3205 (216)	0.64 (0.7261)
		TT	0.6624 (257)	0.6380 (430)	
		T	0.8119	0.7982	0.58 (0.4463)
11	rs2247572 (*KCNB2*), (389/673)	*CC*	0.7172 (279)	0.6746 (454)	
		CT	0.2596 (101)	0.2704 (182)	**6.05 (0.0485)**
		TT	0.0231 (9)	0.0550 (37)	
		C	0.8470	0.8098	**3.95 (0.0468)**
12	rs2616984 (*CSMD1*), (387/673)	*AA*	0.5013 (194)	0.5245 (353)	
		AG	0.3747 (145)	0.3997 (269)	**6.78 (0.0337)**
		GG	0.1240 (48)	0.0758 (51)	
		G	0.3114	0.2756	3.06 (0.0802)
13	rs2252521 (*CPVL*), (389/674)	*CC*	0.5193 (202)	0.5861 (395)	
		CT	0.4165 (162)	0.3561 (240)	4.5 (0.1053)
		TT	0.0643 (25)	0.0579 (39)	
		T	0.2725	0.2359	3.53 (0.0602)
14	rs12807809 (*SPA17/NRGN*), (389/674)	*CC*	0.0411 (16)	0.0312 (21)	
		CT	0.2339 (91)	0.3027 (204)	**6.14 (0.0464)**
		TT	0.7249 (282)	0.6662 (449)	
		T	0.8419	0.8175	2.05 (0.1522)
15	rs2229741 (*NRIP1*), (389/674)	*CC*	0.2725 (106)	0.2760 (186)	
		CT	0.4679 (182)	0.4896 (330)	0.9 (0.6376)
		TT	0.2596 (101)	0.2344 (158)	
		T	0.4936	0.4792	0.41 (0.5219)

N_{case} is the number of individuals diagnosed with schizophrenia; $N_{control}$ is the number of individuals in control group. Statistically significant differences ($p < 0.05$) between case and control group are shown in bold.

constantly circulating in the blood. This cascade system of proteolytic enzymes responsible for humoral immune defense against host agents is involved in the organism's immune response and represents a key component of both congenital and acquired immunity. Studies exploring the role of congenital immunity in schizophrenia were published in Russia, which made it possible to suggest the activation of this immunity type in schizophrenic patients [26]. Other findings demonstrated that the CSMD1 protein could inhibit accumulation of the C3 component in vitro, which resulted in the abnormal functioning and regulation of a classic pathway of complement cascade [27]. Moreover, such proteins involved in the regulation of complement control are known to also affect synaptic functions [28]. The association of *CSMD1* rs2616984 with Alzheimer's disease in the Russian population was previously confirmed by our group [29]. The frequency of the minor *G* allele was significantly higher in individuals with Alzheimer's disease compared to the control group (OR = 1.50; CI: 1.07–2.09; $p = 0.018$).

It should be mentioned that the *CSMD1* gene is located in a genomic region characterized by a high rate of accumulation of modifications in divergence of evolutionary lines of humans and primates [30], which, probably, represents an adaptive role of this genomic region.

Two SNPs (*KCNB2* rs2247572 and intergenic *SPA17/NRGN* rs12807809), which demonstrated

Table 3. Analysis of associations of SNPs with schizophrenia in the Russian population of the Siberian region

No.	SNP ID	Intergenic region, gene	MA	OR	CI	*p* value
1	rs1502844	*SLCO6A1/LINC00491*	*C*	1.14	0.95–1.37	0.1583
2	rs9960767	*TCF4*	*C*	0.68	0.41–1.13	0.1336
3	rs2312147	*VRK2*	*T*	0.99	0.83–1.19	0.9203
4	rs3131296	*NOTCH4*	*T*	0.81	0.60–1.09	0.1583
5	rs1572299	*LOC105376248/LOC105376249*	*C*	0.93	0.78–1.11	0.4424
6	rs17594526	*TCF4*	*T*	0.60	0.25–1.42	0.2384
7	rs1344706	*ZNF804A*	*C*	1.04	0.87–1.26	0.6467
8	rs16977195	*AGBL1*	*G*	0.96	0.67–1.38	0.8414
9	rs7341475	*RELN*	*A*	1.22	0.96–1.53	0.0984
10	rs8020441	*ZFP64P1*	*G*	0.92	0.73–1.15	0.4463
11	rs2247572	*KCNB2*	*T*	0.79	0.62–1.00	**0.0468**
12	rs2616984	*CSMD1*	*G*	1.19	0.98–1.44	0.0802
13	rs2252521	*CPVL*	*T*	1.21	0.99–1.48	0.0602
14	rs12807809	*SPA17/NRGN*	*C*	0.84	0.66–1.07	0.1522
15	rs2229741	*NRIP1*	*T*	1.06	0.89–1.26	0.5219

MA is minor allele; OR is the odds ratio for minor allele; *p* value is the level of significance for OR. Significance level ($p < 0.05$) is shown in bold.

allelic association with schizophrenia, showed associations with a decreased risk of its development.

The mechanisms of the possible involvement of *KCNB2* rs2247572 in disease liability remain unknown. The *KCNB2* gene encodes for the protein of the potential-dependent potassium channel and is required for permeability of potassium ions through the excitable cell membrane. Excitable tissues such as grandular, nervous, and muscular possess such membranes. The channels open and close as a response to difference in tension on the membrane, providing the transport of potassium ions toward their electrochemical gradient.

According to GWAS data, this locus was significantly associated with working memory components including verbal information storage, which is a schizophrenia endophenotyoe [15], as well as with asthma in children from the Mexican population [31]. Interestingly, our previous study reported the association of this SNP with early manifestation of schizophrenia, which was replicated in the Kazakh population [11]. The frequency of a minor *KCNB2* rs2247572 *T* allele was significantly lower in individuals with early manifestation of schizophrenia compared to the control group in the Kazakh population (OR = 0.65; CI: 0.43–0.98; $p = 0.030$). Probably, this gene is related to schizophrenia development and represents a common marker of increased schizophrenia risk in both Caucasoid and Mongoloid populations. No data demonstrating the role of this SNP in schizophrenia development is known.

Another polymorphism previously demonstrating association of heterozygous genotype with schizophrenia is intergenic rs12807809 located in the *SPA17/NRGN* region (OR = 0.70; CI: 0.53–0.94; $p = 0.0464$). According to GWAS, the *T* allele was significantly associated with schizophrenia [4]. At the same time, Rose et al. [32] reported no association of this polymorphism with brain structure peculiarities and behavior in schizophrenic patients from the Irish population.

The published findings frequently relate this SNP to the neurogranin gene (*NRGN*), which is closer than *SPA17* (sperm autoantigenic protein 17). The neurogranin gene (*NRGN*) consists of four exons and three introns. Exons 1 and 2 encode for neurogranin, while exons 3 and 4 contain untranslated sequences. Neurogranin represents the calmodulin-binding protein involved in the protein kinase C signal pathway. It is mainly present in the brain; its frequency is increased in dendrite spines. Neurogranin represents the main postsynaptic calmodulin(CaM)-dependent protein, which binds calmodulin in the absence of calcium, while protein phosphorylation decreases its ability to bind calmodulin. Probably, neurogranin is a direct target for thyroid hormones in the human brain, and control of this gene expression might be the basis of

multiple hypothyreosis consequences affecting human mentality in development and adulthood.

In summary, associations of three polymorphisms located in genes and intergenic regions with schizophrenia for the first time were replicated in the Russian population. Previously, these loci were detected in genome-wide association studies of schizophrenia and its cognitive endophenotypes. Probably, one of the loci, which reported association with a disease, *CSMD1* rs2616984, is common for the development of diseases characterized by impaired cognitive abilities such as Alzheimer's disease, schizophrenia, and bipolar disorder. *KCNB2* rs2247572, which was replicated by our group in different ethnic groups such as Russians and Kazakhs, is probably common for schizophrenia development in both Caucasoids and Mongoloids. Moreover, several loci with differences in distribution of allele frequencies close to a statistically significant level were detected (*RELN* rs7341475, *CSMD1* rs2616984, and *CPVL* rs2252521).

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