Association of Dopamine Receptor D5 Gene Polymorphism with Peculiarities of Voluntary Attention in Schizophrenic Patients and Their Relatives

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We studied the relationship between *DRD5* gene polymorphism presented by microsatellites with cognitive signs in 152 schizophrenic patients, 81 mentally healthy relatives, and 125 mentally healthy control individuals. An association was found between *DRD5* polymorphism with efficiency of visual voluntary attention in patients (p=0.02) and their relatives (p=0.006). Carriers of two copies of the 148-b.p. allele were characterized by low efficiency of attention.

Key Words: *schizophrenia; dopamine D5 receptor gene; attention*

It was demonstrated that dopamine D5 receptors (DRD5) participate in processes related to cognitive functions due to modulation of acetylcholine transmission in the hippocampus and neocortex [2,7]. A relationship was found between *DRD5* gene and mental diseases associated with cognitive disorders, in particular with attention deficit/hyperactivity syndrome (ADHS) and schizophrenia. Comparison of genetic variants determined by microsatellite polymorphism in healthy and ill individuals revealed a significant increase in the frequency of 148 b.p. allele of DRD5 in patients with ADHS and schizophrenia [3,8,9]. We hypothesized that carries of this allele perform cognitive tests worse than carries of other genetic variants.

Here we studied the linkage between DRD5 gene polymorphism and cognitive signs in healthy individuals and patients with schizophrenia.

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MATERIALS AND METHODS

We studied the linkage of DRD5 gene polymorphism presented by microsatellites $(CT/GT/GA)_n$ in the locus adjacent to transcription site with peculiarities of memory and attention in 152 schizophrenia patients (81 men, 71 women, mean age 34.7±12.9 years), in 81 mentally healthy first-degree relatives (38 men, 43 women, mean age 46.3± 14.5 years), and 125 mentally healthy individuals without family history of schizophrenia (71 women, 54 men, mean age 31.8±13.0 years). All examinees signed informed consent for participation in the study. For evaluation of short-term memory, the examinees were asked to remember and repeat as much as possible words read by experimenter. Each examinee was presented 2 series of 10 words. The mean number of reproduced words was evaluated. For evaluation of long-term memory, the examinee was presented 16 words and was instructed to draw a picture for each word which will help to remember these words after 40-60 min. For evaluation of verbal fluency, the examinee was instructed to ge-

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nerate as much as possible words belonging to two different semantic categories. The score was the total number of words. These tests evaluated verbal memory. Attention was evaluated by concentration, *i.e.* by the number of correct operations per minute during serial counting from 200 to 100 by 2 and 5 (test for attention and working memory) and selectivity of attention (the examinee was given a blank with letter rows incorporating words and was instructed to find these words and name them). This test evaluated voluntary visual attention by the number of found words, time of completing the test, and time of finding one word. In schizophrenia patients, psychological testing was performed after improvement of their clinical state. Psychopharmacotherapy was not withdrawn during the tests. For molecular and genetic study, DNA was isolated from the venous blood by phenol-chloroform extraction. Genotyping was performed on an ABI Prism 310 DNA analyzer using SnaPshot ddNTP Primer Extension Kit [6]. Since the studied polymorphism is determined by microsatellites $(CT/GT/GA)_n$ in the locus adjacent to the transcription site and presented by a great number of genotypes formed by at least 14 different alleles, we used currently accepted classification of genotypes. In particular, we compared genotypes including 1 or 2 148-b.p. alleles (in our study it is designated as allele *7*) and genotype containing no this allele.

Statistical processing of the experimental data included comparison of genotype frequencies using Pearson χ^2 test and the efficiency of performance of cognitive tests in individuals with different genotypes. First, using the general linear model we evaluated the effect of the genotype and study group (patients, their relatives, controls) on cognitive signs. The age of examinees served as a covariant. Then, if significant effects were revealed, dispersion analysis in each group was performed. For the group of patients, the severity of clinical symptoms and duration of the disease were used as covariants. A posteriori tests were used for multiple comparisons.

RESULTS

Comparison of genotype distribution revealed no significant differences between the groups (Table 1). Construction of a general linear model where the dependent variable was a composite index including all studied cognitive parameters allowed us to detect the main effect of the group (F=5.3; p=0.0000) and genotype (F=1.7; p=0.028); at the same time, no interaction between these variables were found (F=1.2; p=0.11). When the parameters of verbal memory and parameters of attention were separately included into the model as dependent variables, the main effect of the group (F=5.1; p=0.0000) and genotype (F=1.7; p=0.048) and the effect of their interaction (F=1.6; p=0.023) were observed for the latter case. These effects were most pronounced for parameters evaluating selectivity of attention (p=0.0000 and p=0.01, respectively). Comparison of individual parameters showed that the number of words generated by patients with schizophrenia with genotype containing 2 alleles *7* was lower compared to that in carriers of the genotype with 1 allele 7 (p=0.018). The number of generated words was 12.1±4.2 and 15.7±4.0, respectively. In carriers of genotypes containing no allele *7*, the number of generated words was 14.4±5.7, but this difference from genotype *77* did not attain statistical significance. Similar relationships were observed in relatives of schizophrenic patients: carriers of *77* genotype generated lower number of words than individuals carrying no allele *7* (14.4± 2.8 and 19.4±4.2 words, respectively, p=0.006). In mentally healthy individuals of the control group, no considerable differences between carriers of different genotypes were found.

Thus, general linear model showed that gene *DRD5* participates in cognitive processes in schizophrenia. Polymorphism of *DRD5* gene affects performance of attention tests, in particular, test for selectivity of visual voluntary attention. It should be noted that voluntary attention disorders are typical of schizophrenia pathogenesis [4] and are observed not only in schizophrenics, but also in their relatives [1]. We found that the presence of two copies of allele *7* was associated with lower attention efficiency. These findings agree with the assumption that allele *7* is associated with worse performance of cognitive tests. There is only one report on the relationship between this allele and attention disorders. In children with ADHS, the frequency of this allele was higher in clinical subtype of this syndrome, which is characterized by attention disorders rather than impetuosity [5]. Our findings suggest that in schizophrenia allele *7* is asso-

TABLE 1. Genotype Frequency of Polymorphic Marker $(CT/GT/GA)_n$ *DRD5* in Patients with Schizophrenia, Their Mentally Healthy First-Degree Relatives, and in Control Group

Group	Genotype		
	7$^-$	*7*$^+$	*77*
Control (n=125)	26.4 (33)	48.0 (60)	25.6 (32)
Patients (n=152)	21.7 (33)	52.0 (79)	26.3 (40)
Relatives (n=81)	23.5 (19)	44.4 (36)	32.1 (26)

Note. Number of observations is shown in parentheses.

ciated with impaired attention measured by neuropsychological tests. However, our results are preliminary and require verification in further studies on greater samples and other populations.

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