The study of dopamine receptor genes in patients with schizophrenia

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P.606 CDC42 rs2473317 polymorphism is associated with schizophrenia: A case-control study in the Armenian population

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Background: Schizophrenia is a chronic and severe mental disorder, which is highly heritable [1]. Multiple genetic variants are involved in a polygenic architecture of susceptibility to schizophrenia. Recent studies identified the *CDC42* (cell division cycle 42) as a candidate gene for schizophrenia [2]. CDC42 is a RhoGTPase that is engaged in the outgrowth of the actin cytoskeleton and promotes spine formation. Reduced expression of *CDC42* mRNA in the dorsolateral prefrontal cortex of subjects with schizophrenia has previously been reported [3]. There are number of single nucleotide polymorphisms (SNPs) in *CDC42* gene that may alter its function and expression level. Thus, we have used a candidate polymorphism study approach to identify the possible association of the several functional SNPs in *CDC42* gene (rs2473277, rs2473317 and rs11583790) with schizophrenia in Armenian population.
Methods: In total, 300 unrelated individuals of Armenian nationality were enrolled in this study. Genomic DNA samples of patients and healthy controls were genotyped using polymerase chain reaction with sequence-specific primers. The selection of SNPs was based on their minor allele frequency and functionality. All primers were designed using the reference genomic sequences in the GenBank (Gene ID: 998). Distribution of genotypes for the mentioned SNPs was checked for correspondence to Hardy-Weinberg equilibrium. The significance of differences between study groups in multiplicative, dominant and recessive models was determined using a Fisher's exact test. Nominal *P* values (*Pnom*) were adjusted for multiple testing by Bonferroni correction (factor 3). Corrected *P* values (*Pcorr*) < 0.05 were considered significant.
Results: The genotyping analysis showed that genotype distribution of the *CDC42* gene rs2473277, rs2473317 and rs11583790 SNPs in study groups were concordant with HWE ($P > 0.05$). SNP analysis revealed that rs2473317 variation of the *CDC42* gene is associated with schizophrenia in the multiplicative model (*Pcorr* $= 0.027$, OR $= 0.35$, 95%CI 1.133-2.551) and the recessive model (*Pcorr* $= 0.003$, OR $= 0.074$, 95%CI $0.01-0.572$). Moreover, the frequency of *CDC42* rs2473317*G minor allele was 1.53 (0.151 vs. 0.232, *Pcorr* $= 0.027$) times decreased in schizophrenia patients in comparison with healthy controls. Finally, no associations with schizophrenia were observed for rs2473277 and rs11583790 SNPs of the *CDC42* gene. On the contrary, *CDC42* gene rs2473277 genetic variant was associated with schizophrenia in a recent genome-wide association study [2]. Inconsistency of our data with the published results might be explained due to a long period of isolation of Armenian population since the Bronze Age and subsequently a unique profile of rare disease alleles [4]. From the other side the genetic structure of Armenian population is still largely unknown, which forces as to employ candidate polymorphism approach to study *CDC42*, since its involvement in the genetic susceptibility to schizophrenia is well documented. Furthermore, according to LD analysis results the three studied SNPs of *CDC42* gene are not in strong LD among all groups.
Conclusion: Our findings suggest that the *CDC42* rs2473317*G minor allele might be nominated as a protective against schizophrenia in Armenian population. We suggest that further studies are required to clarify the functional consequences of the mentioned SNP as well as *CDC42* gene in schizophrenia.

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P.607 The study of dopamine receptor genes in patients with schizophrenia

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Background: Schizophrenia is a severe mental disorder, usually treated with long-term anti-dopaminergic therapy. Although several theories have been lanced, pathophysiology of schizophrenia has not yet been elucidated. Identifying genetic factors contributing to development of schizophrenia would be of considerable interest for personalizing treatment [1]. Most studies in the field of pharmacogenetics of schizophrenia are based on the study of receptor candidate genes or secondary messengers (pharmacodynamic components) and that of drug metabolizing enzymes (pharmacokinetic components), or suspected loci to the disease schizophrenia (pathogenetic components).

An important role in personalization of treatment is played by the suitability of drugs targeting dopamine receptors [2].
Objective: to investigate role of 28 SNP's of dopamine receptor genes DRD1, DRD2, DRD2/ANKK1, DRD3, DRD4 as a potential markers of schizophrenia in patients of Russian population.
Methods: Fourhundred and seventy (470) patients with schizophrenia and 127 healthy controls were investigated. Mean age was 42.1 ± 12.4 for patients, for healthy group is 38.5 ± 13.2 years. Mean duration of disease was 13 years for schizophrenic patients. The inclusion criteria were a clinical diagnosis of schizophrenia, according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10: F20), and age 18–75 years old. We used the standard phenol-chloroform method for isolation DNA from whole peripheral blood. Genotyping was carried out on 28 SNPs of dopamine receptors (rs6275, rs1801028, rs4245147, rs134655, rs6277, rs1076560, rs2283265, rs179997, rs6279, rs1076562, rs2734842, rs4532, rs936461, rs2734849, rs11721264, rs167770, rs3773678, rs963468, rs7633291, rs2134655, rs9817063, rs324035, rs1800828, rs167771, rs6280, rs1587756, rs3758653, rs11246226). We were employed the MassARRAY® Analyzer 4 (Agena Bioscience™) and using the kit iPLEX Gold 384. Statistical analysis was carried out with SPSS software, release 17. Statistical significance of tested associations was considered for significance at a P-value less than 0.05.
Results: This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki 1975, revised in Fortaleza, Brazil, 2013), established for experiments involving humans. We recruited patients from three psychiatric hospitals located in the Tomsk, Kemerovo, and Chita oblasts (regions) of Siberia, Russia. Healthy control group was recruited from the same region with identical characteristics, comparable in gender and age. The distribution of genotypes of studied genes corresponded to the Hardy-Weinberg equilibrium. We got statistically significant results for alleles of polymorphic variant rs3773678 of DRD3 receptor gene ($c2 = 4.940$, $p = 0.030$). We found that allele C are significantly associated with protective effect (odds ratio is 0.53 [95% CI: 0.30 - 0.94]) and allele T are significantly associated with predisposing effect on the development of schizophrenia (odds ratio is 1.88 [95% CI: 1.07 - 3.29]).
Conclusion: According to literature data polymorphisms of dopamine receptors genes play important role in the therapy of schizophrenia. A polymorphic variant of one dopamine receptor gene has been identified, whose alleles have predisposing and protective effects for patients in the pathogenesis of schizophrenia.

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P.608 The role of the duration of untreated psychosis in cognitive deficit in schizophrenia - preliminary results

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Cognitive deficit is one of the key symptoms in schizophrenia. Data, however, show significant variability in which cognitive functions are affected and to what extent they have been impaired. Also the course of this deficit is hard to predict because the role of particular factors is not sufficiently understood. This variability might be caused by various factors such as the duration of untreated psychosis (DUP).

The aim of our study was to describe cognitive deficit in first episode of schizophrenia (FES) in relation to the DUP. According to our knowledge, there are no other studies applying the cluster analysis in the FES research. We applied taxonomic approach to cognitive functions to estimate the role of the DUP in the cognitive deficit in FES. To measure the cognitive performance, we used a battery consisting of 16 standard cognitive tests. In 63 healthy controls ($N = 63$) using the Principal Component Analysis our data clustered into 6 cognitive domains: 1) attention and vigilance, 2) speed of processing and psychomotor speed, 3) visual memory and learning, 4) verbal memory and learning, 5) working memory and flexibility, and 6) executive functions and abstraction. This distinction between domains showed to have relatively high reliability (Cronbach alpha $= 0.67-0.82$). We compared these 6 domains in 28 FES patients (10 males, mean age 30,61, $SD = 6,22$) with healthy controls (10 males, mean age 30,75, $SD = 6,22$) paired based on age, sex and education. For all statistical analysis we used the SPSS software and the level of significance 0.05. In FES patients we found three cognitive clusters of impairment: 1) severe deficit in all measured domains, 2) partial deficit – the impairment is found in working memory (not significantly also in the speed of processing and executive functions), and 3) weak impairment or cognitive performance within the average range. Than we correlated the results of these domains with the DUP (post hoc collected data measured in months since the appearance of first symptoms to applying medication). Because of the relatively small sample, we used the non-parametric Kruskal