Background

Pharmacogenetic studies of tardive dyskinesia are very promising direction to develop individualized antipsychotic treatment. Phosphatidylinositol-4-phosphate-5-kinase IIa (PIP5K2A) is one of the key enzymes in phosphatidylinositol-4,5-biphosphate biosynthesis, plays an important role in membrane transduction of neurotransmitter signals and in intracellular signaling. PIP5K2A gene is located in schizophrenia candidate region 10p14-11. Polymorphisms of this gene have been shown to be associated with schizophrenia in European and Chinese populations, but there were no such studies in Russia.

Objective

Our study aimed to investigate association of PIP5K2A polymorphisms with tardive dyskinesia in Russian schizophrenic patients.

Materials and methods

Blood samples from 506 Russian Caucasian patients with clinically established schizophrenia (with an age of 43 15.8 years) were taken in four different psychiatric departments in West Siberia. Abnormal Involuntary Movement Scale (AIMS) was used to assess tardive dyskinesia cross-sectionally. Control group consisted of 198 healthy volunteers. Genotyping of PIP5K2A polymorphisms (rs10828317, rs746203, rs8341) was performed on ABI StepOnePlus with TaqMan Validatee SNP Genotyping Assay (Applied Biosystems). The program SPS11.5 was used for statistical analysis. Hardy–Weinberg equilibrium (HWE) and differences in genotype frequencies were tested using a chi-square test. Comparisons of AIMS-score in different groups were carried out with Kruskal Wallis test.

Results

The genotype distribution of rs10828317, rs746203, rs8341 polymorphism is shown on fig.1. We found no association of rs10828317, rs746203, rs8341 with schizophrenia, but CC-carriers of rs10828317 with schizophrenia had a higher mean AIMS score in comparison to those with the CT or the TT genotype (fig.3). Subsequently, frequency of CC-carriers was significantly higher in group of schizophrenic patients with tardive dyskinesia compared with the group of schizophrenic patients without tardive dyskinesia (OR=2.18 95% CI 1.33 – 3.56 for the CC genotype, fig.2).

Discussion

In figure 4 the SNPs positions are represented. Only one of them, rs10828317, is known to be a functional mutation. Replacement T to C leads to a non-synonymous amino-acid exchange (asparagine-serine) which causes increase of distance between two antiparallel helices from 3A up to 6A and thereby interfere enzyme functioning [1] (fig.5).

Previous studies show that mutant kinase inefficient to activate the KCNQ channels that may lead to lack of dopaminergic control in schizophrenic patients [1]. Moreover, (N251S)PIP5K2A decreased membrane abundance of excitatory amino acid transporter EAAT3 in study on EAAT3-expressing oocytes and human embryonic kidney cells [2]. Taken together, these facts may act as biological explanation of association of (N251S)-PIP5K2A (rs10828317) with tardive dyskinesia.

Conclusions

The significant association of (N251S)-PIP5K2A polymorphism with tardive dyskinesia has been found. CC-carriers with schizophrenia had higher risk of tardive dyskinesia and more severe symptoms as evaluated by AIMS. Further studies are needed to support our findings.

References


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