

Polymorphisms of Akt1 gene in patients with depressive disorders

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ABSTRACT

Protein kinase Akt1 is an important intracellular signaling protein involved in cell proliferation, cell cycle and apoptosis. It is known that Akt1 regulates serotonin and dopamine neurotransmission, BDNF and NGF receptors transmission, inhibits glycogen synthase kinase 3 β (GSK-3 β) activity which makes possible a fact of involvement of Akt1 depression pathogenesis. The aim of this study was to investigate association of two AKT1 gene polymorphisms (rs1130214 and rs3730358) with depressive disorders. 107 DNA samples taken from depressive patients and 103 DNA samples from physically and mentally healthy donors of Caucasian population from Siberia were genotyped. Investigation showed no association of these polymorphisms with depressive disorders in groups. Further investigations of Akt1 gene may enlighten its role in depressive disorders pathogenesis.

Key words: depressive disorders, protein kinase Akt1.

INTRODUCTION

Nowadays, depressive disorders are estimated as pathology with high prevalence and severity. Depression is a serious social-economical burden. In all cases of mental disability, depression leads to disability in 12 % of cases (Krasnov VN, 2011). Recent research showed major role of intracellular signaling pathways dysregulation in pathogenesis of psychiatric disorders (Fedorenko O, Strutz-Seebohm N, Henrion U, Ureche ON, Seebohm G et al., 2008; Fedorenko O, Tang C, Sopjani M, Föllner M, Gehring EM et al., 2009; Ivanova SA, Fedorenko OYu, Smirnova LP, Semke AV, 2013). It is believed that protein kinases involved in neurobiological processes could be possible targets for new methods of pharmacotherapy, prognosis and diagnosis of

affective disorders (Duman R, Voleti B, 2012; Ivanova SA, Semke VYa, Vetlugina TP, Rakitina NM, Kudyakova TA et al., 2007; Losenkov IS, Vyalova NM, Simutkin GG, Ivanova SA, Bokhan NA, 2013; Vyalova NM, Fedorenko OYu, Losenkov IS, Simutkin GG, Ivanova SA et al., 2013). Protein kinase Akt1 is an important intracellular signaling protein involved in cell proliferation, cell cycle and apoptosis. Akt1 regulates serotonin and dopamine neurotransmission, BDNF and NGF receptors transmission, inhibits glycogen synthase kinase 3 β (GSK-3 β) activity which makes it a relevant factor in depression pathogenesis (Beaulieu JM, 2012). Up to date the data of AKT1 gene association with affective disorders is low, and still the role of that gene in this pathology is not clear.

MATERIALS AND METHODS

The group of 107 patients with depressive disorders was included in the study (age from 20 to 60, men – 15.7%, women – 84,3%). Control group consisted of 103 physically and mentally healthy donors (age from 20 to 50, men – 14.3%, women – 85,7%). All participants were Caucasians from Siberia (Tomsk, Tomsk Region, Russia). After approval of the study protocol by the Institutional Medical Review Board, patients were recruited from Affective States Department of Mental Health Research Institute SB RAMSci's clinics. Main criteria were clinically verified diagnosis of depressive episode (ICD-10: F32) (54 patients) and recurrent depressive disorder (ICD-10: F33) (53 patients), Caucasian race, absence of organic or neurological pathology. Venous blood samples were taken in the morning after fasting from forearm vein in vacuum tubes with EDTA. Absorbed method kit (Medigen, Russia) for DNA extraction was used. Two single nucleotide polymorphisms (SNP) rs1130214 and rs3730358 of AKT1 gene were genotyped using real-time PCR with TaqMan® SNP Genotyping Assay kits (Applied Biosystems, USA) and StepOne Plus real-time amplifier (Applied Biosystems, USA). Statistical

analysis was performed using SPSS software (v.20.0). The Hardy-Weinberg equilibrium of genotyping frequencies was tested by the chi-square test. The chi-square test was used for between-group comparison of genotypes frequencies. Significance was set at $p < 0.01$.

RESULTS AND DISCUSSION

Genotyping of SNP rs1130214 showed findings as follows (see Fig. 1). In the control group, genotype frequencies were A/A – 9.2%, A/C – 45.0%, C/C – 45.8%, which was in agreement with Hardy-Weinberg equilibrium ($X^2=0.190$, $p=0.662$). In the group of patients, genotype frequencies were A/A – 9.0%, A/C – 38.6%, C/C – 52.4%, that was also in agreement with Hardy-Weinberg equilibrium ($X^2=0.331$, $p=0.564$). Frequency of allele A in a group of healthy donors was 31.7% and 28.3% in group of patients. Frequencies of allele C in groups of patients and healthy donors were 62.9% and 71.7%, respectively. No difference between groups in observed frequencies of genotypes ($X^2=1.222$, $p=0.804$) and alleles ($X^2=0.660$, $p=0.420$) of SNP rs1130214 was found.

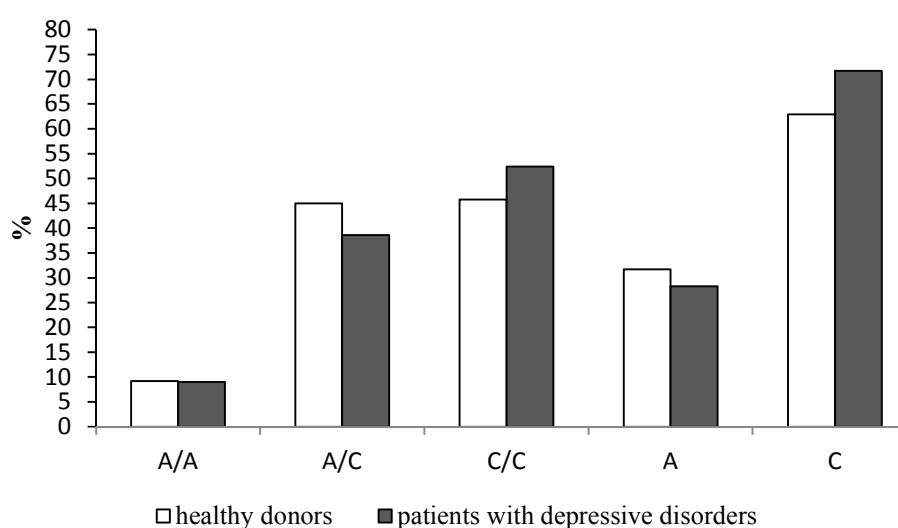


Figure 1. Distribution of genotypes and alleles of SNP rs1130214 of AKT1 gene in groups of healthy donors and patients with depressive disorders

Genotyping of SNP rs3730358 showed no difference between groups in genotypes ($X^2=0.058$, $p=0.841$) or alleles distribution ($X^2=0.050$, $p=0.830$) (see Fig. 2). In both control group ($X^2=0.116$, $p=0.733$) and group of patients ($X^2=0.057$, $p=0.801$) deviation from Hardy-Weinberg equilibrium was not found. Frequencies of genotypes in control group were A/A – 2.2%, A/G – 28.3%, G/G – 69.5% and in a group of patients – A/A – 2.6%, A/G – 28.8%, G/G – 68.6%. Frequency of allele A in the group of healthy donors was 16.3%, and 17.0% in group of patients. Frequencies of allele C in groups of patients and healthy donors were 83.7% and 83.0%, respectively.

Therefore our research showed no association between SNP rs1130214 and rs3730358

of AKT1 gene and depressive disorders. Nowadays, there are a small number of studies devoted to AKT1 gene association with affective disorders and most works about AKT1 gene association are made for schizophrenia [3]. SNP rs1130214 and rs3730358 are associated with low level of Akt1 in prefrontal cortex which makes them particularly interesting [4]. In the work of F. Kagere et al. association of these two SNPs with bipolar disorder (BD) was demonstrated [9]. L. Magno et al. showed association of SNP rs1130214 with suicidal behavior in BD patients [12]. In the work of P. Pereira et al. it was shown that SNP rs3730358 was associated with late-life depression [13]. All these results indicate that SNP rs1130214 and rs3730358 could be important in pathogenesis of affective disorders. Further studies are needed.

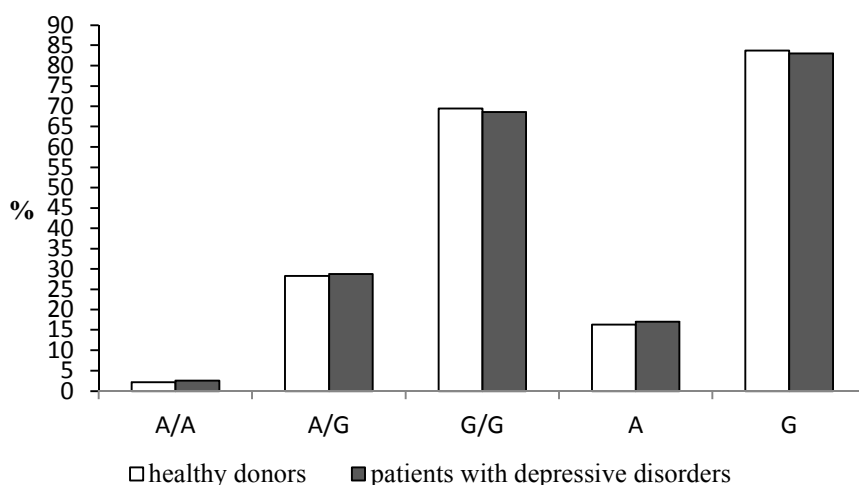


Figure 2. Distribution of genotypes and alleles of SNP rs3730358 of AKT1 gene in groups of healthy donors and patients with depressive disorders

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