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Analysis of common pharmacokinetic and pharmacodynamic gene polymorphisms in a sample of Bulgarian outpatients with recurrent depression

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Major depression (MDD) is a multi-gene multifactorial complex disorder and after years of extensive genetic research, no reliable single-gene predictor of clinical course is yet generated. Interaction of genes encoding metabolic proteins and controlling drug targets is supposed to play a role in both pathogenesis of depression and treatment response, but genomic data are still controversial. Recent studies have reassessed the hypothesis of genetic-based differences in transcriptional regulation of neurotrophins and their influence on neuronal plasticity and behavioral pattern, but the exact mechanisms of gene-gene and gene-environment interplay with MDD are largely unidentified.

This study aimed to investigate the genotype and allele frequencies of common polymorphic pharmacokinetic and pharmacodynamic genes and their association with MDD in a sample of Bulgarian outpatients with recurrent depression compared to healthy controls.

A total of 100 white Bulgarian unrelated patients with recurrent depression (31% males and 69% females; mean age 45.58 ±11.09) and 142 psychiatrically healthy controls (35% males and 65% females; mean age 47.54 ±12.09) were genotyped for 9 variants in 5 genes: insertion/deletion variant (5-HTTLPR) and functional SNP (rs25531) within serotonin transporter promoter, and intron 2 VNTR (Stin2 VNTR) in SLC6A4 gene; CYP2D6*4, CYP2C19*2 and CYP2C19*17 variants in cytochrome P 450 genes; Val66Met, rs12273363 and rs16917237SNPs in BDNF gene. The study was supported by a grant of Medical University-Pleven (No18/2012) and approved by the Ethics committee. A written informed consent was obtained a priory. Genomic DNA was isolated from whole blood via salting out procedure. The CYP2D6*4 allele was detected by PCR amplification (adapted by Heim and Meyer). The CYP2C19*2 and *7 variants were genotyped by high-resolution melting curve analysis (Qiagen Rotor Gene Q). The SLC6A4 variants were amplified by PCR (optimized Wendland, et al. Protocol). A TaqMan method was used for genotyping of BDNF SNPs.

Distributions of all tested genotype and allele frequencies were in accordance with Hardy-Weinberg equilibrium. The genotype distributions were: for 5-HTTLPR long (L) and short(S) variant – 39% L/L, 41% S/L, 20% S/S (patients), and 28% L/L, 50% S/L, 22% S/S (controls) ($p=0.52$); for rs25531 – 34% LA/LA, 34% LA/SA, 18% SA/SA; 4% LG/SA and 7% LG/LA (patients), and 29.6% LA/LA, 44.4% LA/SA, 19.7% SA/SA; 3.5% LG/SA, 2.8% LG/LA (controls) ($p=0.24$, for LG/LA $p<0.05$); for STin2 – 32% 12/12, 43%10/12, 13.14% 10/10 (patients), and 37.23% 12/12, 49.64% 10/12, 20% 10/10 (controls). The 9/10 (3%) and 9/12 (2%) genotypes were found only in the patient group ($p=0.036$). CYP2D6*4 allele was identified in 41% of patients. CYP2D6*4 distribution in the study sample was not significantly different from estimated for Bulgarian population (Saraeva R. 2008). No significant difference was found for the genotyped BDNF variants in both groups.

In summary, our study found an association of rs25531 LG/LA genotype with MDD in the sample of Bulgarian outpatients with recurrent depression. A tendency was found for higher distribution of 5HTTLPR L/L and STin2 9/10 and 9/12 in patients. Further larger studies would clarify our research suggestions.