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The kynurenine pathway in major depression: Haplotype analysis of three related functional candidate genes

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ABSTRACT

A consistent finding in major depressive disorder (MDD) research is dysfunction of the immune system. One of the relevant metabolic pathways in this regard is the kynurenine pathway. In patients with major depression, an imbalance between neuroprotective and neurotoxic arms of the pathway with lower plasma kynurenic acid concentration was demonstrated. Therefore, we investigated Single Nucleotide Polymorphism (SNP) and haplotype association of three candidate genes of the three enzymes involved in this metabolism. The three genes, namely, tryptophan hydroxylase 2 (TPH2), kynurenine 3 monooxygenase (KMO) and kynurenine amino transferase 3 (KAT III) SNPs and haplotype association analysis was performed in 338 (266 major depression and 72 bipolar depression) unrelated Caucasian patients with major depressive episodes and 310 age, gender and ethnicity matched controls. In sliding window analyses using PLINK of the haplotypes of KAT III, all windows which include the first SNP (rs12729558), the overall haplotype distribution (OMNIBUS) was significantly different between patients with a major depressive episode and control for all windows, with p-values ranging between $1.75 \times 10 = 5$ and 0.006. This is due to the haplotype CGCTCT (referring to 6 SNP window analysis), which is found in about 5.7% of patients and 1.9% of healthy controls. It was due to CGCTCT haplotype and the frequencies of this haplotype in both bipolar patients and patients with major depression showed significantly higher than the control population ($p<0.001$). This haplotype of KAT III gene CGCTCT may have effect on the function of this enzyme in formation of kynurenic acid in some patients with major depressive episodes.