Interaction among childhood trauma and functional polymorphisms in the serotonin pathway moderate the risk of depressive disorders

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Depressive disorders are influenced by a complex interplay between genetic and environmental factors. Multiple studies support a role of serotonergic pathways in the pathophysiology of depressive disorders. As a rate-limiting enzyme of serotonin synthesis in the brain, tryptophan hydroxylase 2 (TPH2) represents a plausible candidate gene. This also applies to the serotonin reuptake transporter (5-HTTLPR) regulating the availability of serotonin in the synaptic gap. We hypothesize that functional polymorphisms (TPH2: rs7305115, 5-HTTLPR and rs25531) within both genes contribute to the risk of depressive disorders after childhood abuse in adult life. To confirm our results, we investigated two independent samples of Caucasian subjects from the study of health in Pomerania (SHIP-LEGEND: n=2,029 and SHIP-TREND-0: n=2,475). Depression severity was assessed by the Beck depression inventory (BDI-II) for LEGEND and the patient health questionnaire (PHQ-9) for TREND-0. Childhood abuse was assessed by the childhood trauma questionnaire. Rs7305115 (TPH2) revealed significant effects in SNP*abuse and SNP*SNP as well as in the three-way interaction. This three-way interaction among abuse, TPH2 and 5-HTTLPR showed a significant effect on depression score (p=0.023). The SS genotype of 5-HTTLPR was associated with increased depression scores after childhood abuse only in carriers of the low-expression TPH2 GG genotype, whereas the TPH2 AA genotype reversed this effect. Our results support the role of interaction effects of genetic variants within serotonergic pathways. Genetic variants that may decrease the presynaptic serotonin concentration were associated with increased adult depressive symptoms in subjects with childhood abuse.
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