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Interaction between *COMT* and *MTHFR* genetic variants protect against risk for bipolar II disorder in Han Chinese

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Objectives: Bipolar II disorder (BP-II), characterized by recurrent dysregulation of mood, is a serious and chronic psychiatric illness. However, BP-II is commonly under-recognized, even in psychiatric settings. Because dopaminergic disturbance is thought to be involved in the development of bipolar disorder (BPD), it seems essential to investigate dopamine-related genes like the catechol-O-methyltransferase (*COMT*) gene, which are involved in dopamine metabolism, and the methylenete trahydrofolate reductase (*MTHFR*) gene, which may affect COMT methylation and COMT function. The current study examined the association and interaction of the *COM*T Val158Met and *MTHFR* C677T variants with BP-II.

Methods: Nine hundred seventy-eight participants were recruited: 531 with BP-II and 447 healthy controls. The genotypes of the *COMT* and *MTHFR* polymorphisms were determined using a polymerase chain reaction-restriction fragment length polymorphism analysis.

Results: After the *MTHFR* C677T genotypes in BP-II patients and Controls had been stratified, the COMT Val/Val variant was significantly more frequently detected in controls than in BP-II patients (P=0.008). Logistic regression analysis showed a significant interaction effect of the *COMT* Val158Met Val/Val genotype and the *MTHFR* C677T C/T+T/T genotype (OR=0.57, P=0.039) for the protective effect on the odds of developing BP-II.

Conclusion: Our findings support preliminary evidence that the *COMT* and *MTHFR* genes interact in BP-II, and they imply the connection of both dopaminergic pathways and methylation pathways in the pathogenesis of BP-II.

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