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Association between 5HTT, DAT1, and DRD4 and bipolar disorder in youth

Victoria E. Cosgrove, Ph.D.^{1,2,3}, David J. Miklowitz, Ph.D.^{2,4}, Soo Hyun Rhee, Ph.D.^{2,3}, Christopher Hawkey, B.A.², Robin Corley, Ph.D.³, Brett Haberstick, Ph.D.³, and Andrew Smolen, Ph.D.³

¹ Pediatric Bipolar Disorders Research Program, Stanford University School of Medicine

² Department of Psychology and Neuroscience, University of Colorado at Boulder

³ Institute for Behavioral Genetics, University of Colorado at Boulder

⁴ Semel Institute for Neuroscience and Behavior, University of California at Los Angeles

Bipolar disorder (BD) in youth is characterized by rapid fluctuation between high and low mood states, severe irritability, and multiple psychiatric comorbidities. Left untreated, affected youth may demonstrate compromised development in social, neurobiological, cognitive, and emotional realms (Miklowitz & Cicchetti 2006). Given the marked genetic loading associated with pediatric BD (Leibenluft 2008), identifying genetic risk profiles may prove critical for understanding its onset. The present study examined relationships between BD in youth and the 5HTT-linked polymorphic region (5HTTLPR) in the serotonin transporter (5HTT, SLC6A4), a 40-base pair Variable Number Tandem Repeat (VNTR) polymorphism in the 3' untranslated region of the dopamine transporter (DAT1, SLC6A3), and a 44-base pair VNTR in exon 3 of the dopamine D4 receptor (DRD4). Given possible relevance of age, we also examined interaction effects of age and genotype on symptoms of depression in youth with BD.

Genomic DNA was collected from youth meeting DSM-IV criteria for BD I, II, or Not Otherwise Specified (n=62) recruited in a research clinic at the University of Colorado at Boulder and controls (n=239) from the Colorado Twin Registry. All loci were in Hardy-Weinberg equilibrium. 5HTTLPR ($\chi^2=1.79$, df=2, p=.41; cases: short/short (S/S)=8, long/long (L/L)=22, S/L=32, controls: S/S=48, L/L=78, S/L=110), DAT1 3' UTR VNTR ($\chi^2=1.51$, df=2, p=.47; cases: S/S=5, L/L=34, S/L=22, controls: S/S=12, L/L=124, S/L=102), and DRD4 VNTR ($\chi^2=.05$, df=2, p=.97; cases: S/S=38, L/L=3, S/L=19, controls: S/S=149, L/L=11, S/L=79) did not show significant association with DSM-IV BD. The lack of inclusion of the L_A/L_G 5HTTLPR SNP (Hu et al. 2005) was a limitation of the present study.

Regression models including age, genotype, and their interaction significantly predicted Depression Rating Scale (DRS; Kaufman et al. 1997) scores in youth with BD for 5HTTLPR (F=3.46, df=3, p=.02) and DRD4 (F=3.76, df=3, p=.02). Effects of age (5HTTLPR: t=2.83, p=.01; DRD4: t=2.02, p=.05) and age x genotype interaction (5HTTLPR: t=2.59, p=.01; DRD4: t=2.59, p=.01) were significant; for both, DRS scores increased more steeply with progressing age as the number of L alleles increased.

In summary, we found no evidence of an association between 5HTT, DAT1, and DRD4 and DSM-IV BD but evidence of a genotype x age interaction effect for 5HTT and DRD4 on a measure of depressive symptoms in youth with BD spectrum disorders. Since 5HTT, DAT1, and DRD4 have been linked with BD in adults (Escamilla & Zavala 2008), symptoms common in youth (e.g., irritability) may show weaker associations with these markers than those more frequently observed in adult BD (e.g., elevated mood, hypersexuality, grandiosity). Depression in pediatric BD may worsen in part as a function of genotype as youth get older and approach adulthood. Whereas the L variant of the DRD4 VNTR appears to react less strongly to dopamine molecules linked to the brain's reward system, the 5HTTLPR L allele is thought to lead to greater transport of serotonin which is associated with regulation of emotions and drives. The effect of dopaminergic and serotonergic gene expression on depressive symptoms in youth may change with age.

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