Leveraging pleiotropy with bipolar and associated disorders to improve discovery of genetic associations in ADHD

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Attention Deficit/hyperactivity disorder (ADHD) is a condition characterized by problems with inattention, hyperactivity and/or impulsivity affecting between 6-12% of children worldwide¹. These symptoms are often disruptive, impairing performance in broad aspects of one’s life including academic, intellectual, and social settings, as well as while driving¹. The etiology of the disorder is accepted as multifactorial. Environmental factors, such as low socioeconomic status and familial instability, constitutional factors, such as gender and age, as well as a strong genetic component (heritability = 0.75) confer risk for ADHD¹. Some of these risk factors may be shared as substantial psychiatric and behavioral comorbidities have been reported¹,². Notable are reports of comorbid and co-segregation/aggregation within families of ADHD probands of Bipolar Disorder²,³,⁴, the exact cause of which is unresolved.

Despite the high heritability, genome-wide linkage and association studies have revealed few consistent genetic signals. While a number of candidate genes have shown consistent associations with ADHD¹, their effects sizes are modest and in aggregate they explain little of the heritability. It is likely that the genetic architecture of ADHD is highly polygenic, composed of many genetic factors, each conferring a small amount of risk.

Using the results of the largest ADHD and Bipolar genome-wide association studies (GWAS) and novel statistical approaches that leverage pleiotropy, or shared genetic effects, and functional annotations of genetic variants to improve the power of GWAS⁵,⁶ we demonstrate shared genetic associations between ADHD and Bipolar Disorder. This suggests some of the co-appearance of the disorders may be due to shared genetic factors. Further, we report novel candidate variants for ADHD garnered from the improved power of the pleiotropy and annotation informed genetic analyses and discuss their implications in the etiology of ADHD.