

Genetic Overlap Between Attention-Deficit/Hyperactivity Disorder and Bipolar Disorder: Evidence From Genome-wide Association Study Meta-analysis

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ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BPD) are frequently co-occurring and highly heritable mental health conditions. We hypothesized that BPD cases with an early age of onset (≤ 21 years old) would be particularly likely to show genetic covariation with ADHD.

METHODS: Genome-wide association study data were available for 4609 individuals with ADHD, 9650 individuals with BPD (5167 thereof with early-onset BPD), and 21,363 typically developing controls. We conducted a cross-disorder genome-wide association study meta-analysis to identify whether the observed comorbidity between ADHD and BPD could be due to shared genetic risks.

RESULTS: We found a significant single nucleotide polymorphism-based genetic correlation between ADHD and BPD in the full and age-restricted samples ($r_{\text{Gfull}} = .64, p = 3.13 \times 10^{-14}$; $r_{\text{Grestricted}} = .71, p = 4.09 \times 10^{-16}$). The meta-analysis between the full BPD sample identified two genome-wide significant ($p_{\text{rs7089973}} = 2.47 \times 10^{-8}$; $p_{\text{rs11756438}} = 4.36 \times 10^{-8}$) regions located on chromosomes 6 (*CEP85L*) and 10 (*TAF9BP2*). Restricting the analyses to BPD cases with an early onset yielded one genome-wide significant association ($p_{\text{rs58502974}} = 2.11 \times 10^{-8}$) on chromosome 5 in the *ADCY2* gene. Additional nominally significant regions identified contained known expression quantitative trait loci with putative functional consequences for *NT5DC1*, *NT5DC2*, and *CACNB3* expression, whereas functional predictions implicated *ABLIM1* as an allele-specific expressed gene in neuronal tissue.

CONCLUSIONS: The single nucleotide polymorphism-based genetic correlation between ADHD and BPD is substantial, significant, and consistent with the existence of genetic overlap between ADHD and BPD, with potential differential genetic mechanisms involved in early and later BPD onset.

Keywords: Attention-deficit/hyperactivity disorder, bipolar disorder, cross-disorder meta-analysis, genetic correlation, genetic overlap, GWAS

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Attention-deficit/hyperactivity disorder (ADHD) is the most frequent neuropsychiatric disorder in childhood and frequently persists into adulthood. Bipolar disorder (BPD) is among the most prevalent mental diseases in adulthood. Both disorders are highly heritable (1,2). However, in both cases the mode of inheritance is complex and polygenic (3). Although differing from one another with regard to core signs and symptoms, age of onset, presentation, and treatment response, the two disorders share several clinical features. This is especially the case for the manic phase of BPD, which is associated with irritability, increased impulsivity, distractibility, and restlessness (4). Furthermore, ADHD often copresents with depression (5), a core feature of BPD. In adulthood, when BPD is most commonly diagnosed, co-occurrence of the two disorders

occurs more often than would be expected by chance (6). For patients with BPD rates of ADHD vary between 9.5% and 28%, depending on study characteristics (7,8). The rate of BPD in adult ADHD has been estimated at around 20% (7). Meta-analyses of family studies confirm elevated rates of BPD in first-degree relatives of ADHD patients and vice versa (8).

Although a shared genetic basis for ADHD and BPD seems plausible given the above, molecular genetic studies thus far provide limited evidence for this (9–11). For instance, risk-allele frequencies of candidate genes, identified through prior ADHD genome-wide association studies (GWASs), are not increased in BPD. This failure to find a shared genetic signal may be due to prior studies' lack of statistical power and to the limited set of polymorphisms examined. To address these shortcomings,

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a genome-wide cross-disorder meta-analysis of BPD and ADHD was conducted in a large sample of individuals with BPD, individuals with ADHD, and in typically developing control subjects from the Psychiatric Genomics Consortium. Because ADHD is a childhood onset disorder (prior to 12 years of age), we hypothesized that the overlap would be most obvious in BPD cases with a relatively early onset (age of onset ≤ 21 years old), as this group could be assumed to have a more neurodevelopmental etiology (8). Restricting the age range of the sample to those with an onset ≤ 21 years of age may also increase the power for gene finding because it could reduce heterogeneity (12). We thus performed analyses with the total number of BPD cases as well as the age-restricted set. GWAS meta-analysis top findings were further characterized using expression quantitative trait locus (eQTL) analysis to investigate potential functional consequences for gene expression.

METHODS AND MATERIALS

Samples

Cases, controls, and family-based samples assembled for previous genome-wide Psychiatric Genomics Consortium analyses of individual-level data were included in the current analysis (13,14). A description of individual study data contributions and genotyping platforms is included in [Supplemental Tables S1A and S1B](#). The ADHD sample comprised 4609 cases and 8519 controls. The full BPD sample comprised 9650 cases and 12,844 controls. For tests of the age of onset hypothesis we restricted the BPD sample to cases with an age of onset ≤ 21 years of age. This reduced the number of cases to 5167 (restricted sample). All available controls from the BPD samples were included in the age-restricted sample to maximize power. Control individuals that featured in both the ADHD and BPD samples were identified and removed prior to analysis.

Genetic Analysis

Raw genotype and phenotype data for each study was uploaded to a central server and processed through the same quality control, imputation, and analysis process to ensure comparability between the samples. The quality control and analysis pipeline is described elsewhere (3).

Statistical Analysis

Linkage disequilibrium (LD) score regression was used to estimate the single nucleotide polymorphism (SNP)-based genetic correlation (r_G) between the ADHD and both BPD samples. For LD score regression, each data set underwent additional filtering. Only markers overlapping with HapMap Project Phase 3 SNPs and passing the following filters were included: INFO (imputation) score > 0.9 , study missingness of 0, and minor allele frequency $> 1\%$ (where available). Indels and strand-ambiguous SNPs were removed.

The analysis was conducted using a two-step procedure with the LD scoring analysis package (<https://github.com/bulik/ldsc>) (15). An unconstrained regression was run to estimate the regression intercepts for each phenotype, followed by an analysis with regression intercepts constrained to

those estimated in the first step and an unconstrained covariance intercept (we took steps to exclude overlapping samples). Standard errors were estimated using a block jackknife procedure and used to calculate p values.

GWAS was initially performed for each ADHD study separately ($n = 8$). Four multidimensional scaling components were included to account for potential population stratification. GWAS was then also performed for each BPD study separately ($n = 12$). In this case a total of seven multidimensional scaling components (both total and restricted samples) were used in the analysis in order to correct for potential population stratification. These GWASs were free from genomic inflation as judged by quantile-quantile plots (data not shown). For each disorder, results were then combined in a disorder-specific meta-analysis. Finally, results from the disorder-specific meta-analyses were combined in cross-disorder meta-analyses for both the primary and the age-restricted samples. For all meta-analyses, we applied a weighted Z-score approach using PLINK 1.07 (<http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml>), in which weights equaled the inverse of the regression coefficient's standard error (16). This strategy assumed a fixed-effects model, in which all studies/disorders had the same direction of effect, with weights indicating the sample size and imputation accuracy of the disease-specific studies. The fixed effects model was compared with a genome-wide random-effects model in which studies/disorders were allowed to have a different direction of effect.

Prediction of Allele-Specific Effects on Transcription

The overlap between polymorphic loci with microRNA binding sites was examined using the PolymiRTS 3.0 database (17). To check for the known influence of identified SNPs on gene expression, we searched a database of cis-acting eQTLs defined with RNA sequencing data of lymphoblastoid cell lines from 462 individuals, most of which were also examined in the 1000 Genomes Phase I dataset (18). Allele-specific transcription factor binding sites (TFBSs) were predicted with the web-based tool MatInspector version 2.1 (http://www.genomatix.de/online_help/help_matinspector/matinspector_help.html) (19). TFBS searches were performed for all promoter regions (40 kb upstream) of the top 100 SNPs identified in the full and the age-restricted meta-analyses (i.e., each allele flanked by 10 base pairs up- and downstream sequence). Sequences with a transcription factor-specific matrix core similarity of at least 0.75 were defined as potentially containing the respective TFBS.

RESULTS

SNP-Based Genetic Correlation

The SNP-based r_G between ADHD and BPD was substantial and significant for both the full and age-restricted samples. Interestingly, the r_G was higher for the age-restricted sample as compared with the full sample ($r_{G\text{full}} = .64$, $SE = .02$, $p = 3.13 \times 10^{-14}$; $r_{G\text{restricted}} = .71$, $SE = .02$, $p = 4.09 \times 10^{-16}$; [Table 1](#)).

Full Sample. [Figure 1A](#) shows the Manhattan plot of the primary cross-disorder meta-analysis, and [Supplemental](#)

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