Identification of Genetic Overlap and Novel Risk Loci for Attention-Deficit/Hyperactivity Disorder and Bipolar Disorder

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Abstract

Differential diagnosis between childhood onset attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) remains a challenge, mainly due to overlapping symptoms and high rates of comorbidity. Despite this, genetic correlation reported for these disorders is low and non-significant. Here we aimed to better characterize the genetic architecture of these disorders utilizing recent large genome-wide association studies (GWAS). We analyzed independent GWAS summary statistics for ADHD (19,099 cases and 34,194 controls) and BD (20,352 cases and 31,358 controls) applying the conditional/conjunctional false discovery rate (condFDR/conjFDR) statistical framework that increases the power to detect novel phenotype-specific and shared loci by leveraging the combined power of two GWAS. We observed cross-trait polygenic enrichment for ADHD conditioned on associations with BD, and vice versa. Leveraging this enrichment, we identified 19 novel ADHD risk loci and 40 novel BD risk loci at condFDR < 0.05. Further, we identified five loci jointly associated with ADHD and BD (conjFDR < 0.05). Interestingly, these five loci show concordant directions of effect for ADHD and BD. These results highlight a shared underlying genetic risk for ADHD and BD which may help to explain the high comorbidity rates and difficulties in differentiating between ADHD and BD in the clinic. Improving our understanding of the underlying genetic architecture of these disorders may aid in the development of novel stratification tools to help reduce these diagnostic difficulties.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a childhood-onset and a childhood prevalence of approximately 3-5% [1, 2], with the rate of persistence into adulthood estimated at 15-65% [3]. ADHD is associated with psychosocial disability and societal costs [4]. The most prominent features of ADHD are attentional dysfunction, hyperactivity and impulsivity. Affected individuals may also experience additional neuropsychological difficulties associated with memory [5], executive functioning [6] and emotional dysregulation [7]. In contrast to ADHD, bipolar disorder (BD) has a peak prevalence rate in the early 20s and decreases with age thereafter [8]. This disorder affects approximately 2% of the population when considering both BD I and II types [9]. Moreover, BD is characterized by recurrent episodes of mania and depression, affecting thought, perception, emotion, cognitive function and social behaviour [8].

Differential diagnosis between ADHD and BD, which relies on clinical observation and parental/school reporting, remains a challenge [10, 11]. This is due to factors such as extensive symptom overlap, reciprocal comorbidity, as well as the overlapping range in age of onset, retrospective parental reports and non-episodic course of BD in youths[10, 11]. It is estimated that approximately 20% of adult patients with ADHD have comorbid BD [10], and between 10-30% of adults affected with BD present with comorbid ADHD [12–14]. This relationship has been confirmed in a number of epidemiological, neuroimaging and family studies, however the mechanisms behind this association are not fully understood [15]. Given the high heritability of these disorders [16, 17], numerous studies attempted to identify a shared genetic basis that might

explain the high comorbidity rate [18–20]. The complex polygenic nature of these disorders and the limited statistical power of the available genetic studies have, however, yet provided no clear evidence for genetic overlap.

More recently, a genome-wide cross-disorder meta-analysis of ADHD and BD, using moderately powered GWAS samples [21, 22], identified shared risk loci for these disorders [23]. Subsequent to these findings, GWAS studies with larger sample sizes and greater statistical power have identified many more significant loci for both ADHD [24] and BD [25], however genome-wide genetic correlation between these disorders was low and non-significant ($r_g = 0.095$, $p = 0.081$) [24]. One pitfall in the LD-score regression-based estimates of genome-wide genetic correlation is that the method relies on consistent effect directions of the overlapping variants for the phenotypes of interest [26]. Recent evidence suggests mixed patterns of effect directions for the variants shared between diverse phenotype pairs [27–34]. Such patterns may explain the low genome-wide genetic correlation identified between ADHD and BD, and thereby highlight the usefulness of improved statistical approaches suitable for disentangling the complex genetic relationship of these disorders.

The aim of the current study was to investigate the genetic relationship between ADHD and BD by applying a conditional/conjunctional false discovery rate (condFDR/conjFDR) approach [35, 36]. This approach increases the power to detect novel phenotype-specific and shared loci by leveraging the combined power of two GWAS, and has been used previously to identify novel and shared loci for a number of complex traits and disorders [27, 29, 32, 35–41]. Based on the

clinical and epidemiological findings, we hypothesized to discover polygenic overlap as well as shared genetic loci between ADHD and BD.

Methods and Materials

GWAS Samples

GWAS summary statistics for ADHD and BD were obtained from the Psychiatric Genomics Consortium (PGC). The ADHD sample comprised 19,099 cases and 34,194 controls from 12 cohorts [24], while the BD sample comprised 32 cohorts with 20,352 cases and 31,358 controls [25]. The BD cases included 14,879 individuals with a diagnosis of BD type I (BD1), 3,421 with BD type II (BD2), 977 with schizoaffective disorder, bipolar type (SAB), and the remaining with unspecified BD [25]. The Norwegian Institutional Review Board for the South-East Norway Region has evaluated the current protocol and found that no additional institutional review board approval was needed because no individual data were used. More detailed descriptions are available in the Supplementary Methods and original publications [24, 25].

Statistical Analyses

We generated conditional QQ plots in order to visually assess the cross-phenotype polygenic enrichment, conditioning ADHD on BD and vice versa. QQ plots depict the quantiles of the observed p-values on the y-axis against the theoretical quantiles under no association on the x-axis. Such QQ plots follow a straight line in the case of no association, but deflect from this line when some form of systematic association is present. Conditional QQ plots depict the differential enrichment between pre-specified strata of single nucleotide polymorphisms (SNPs). The data points on the QQ plot are weighted according to the LD structure around the corresponding SNP. We used n=200 iterations of random pruning with an LD threshold r2=0.1 to define LD-blocks throughout the genome. For each iteration, only one SNP from each block was selected to

contribute to the p-value distribution statistics. The procedure entails the selection of a primary trait (e.g. ADHD) and the definition of SNP strata based on a secondary conditional trait (e.g. BD). We plotted the SNP p-values of the primary trait conditional on different strengths of association with the secondary trait (i.e. −log10 p- values > 1, 2, or 3). This enabled us to determine if conditioning on a secondary trait leads to stronger association in the primary trait. A stronger enrichment together with increased evidence for association with the secondary trait can be an indicator of a shared polygenic architecture between the two traits. As a means for comparison, we also estimated the genetic correlation between these ADHD and BD samples [26, 42].

To identify shared loci between ADHD and BD we employed the condFDR/conjFDR method [35, 36]. The condFDR method utilizes genetic association summary statistics from a trait of interest (ADHD) together with those of a conditional trait (BD) to estimate the posterior probability that a SNP has no association with the primary trait, given that the p-values for that SNP in both the primary and conditional traits are lower than the observed p-values. This method increases the power to identify loci associated with the primary trait by leveraging associations with conditional traits, thereby re-ranking SNPs compared to the original GWAS p-value ranking. The conjFDR statistic is defined as the maximum of the two mutual condFDR values and is a conservative estimate of the posterior probability that a SNP has no association with either trait, given that the p-values for that SNP in both the primary and conditional traits are lower than the observed p-values. The conjFDR method thus allows the identification of loci associated with both traits. An FDR level of 0.05 per pair-wise comparison was set for condFDR and conjFDR. P-values were corrected for inflation using a genomic inflation control procedure

[35]. All code used for carrying out the described analyses is available online (https://github.com/precimed/pleiofdr). More details about the condFDR/conjFDR methods can be found in the original and subsequent publications [27, 29, 32, 35–41, 43], and the Supplementary Methods.

Genomic loci definition

Independent genomic loci were defined according to the FUMA protocol [44]. First independent significant SNPs were identified as SNPs with condFDR/conjFDR < 0.05 and linkage disequilibrium (LD) $r^2 < 0.6$ with each other. A subset of these SNPs (LD $r^2 < 0.1$) were then selected as lead SNPs. The borders for genomic loci were then defined by identifying all candidate SNPs in LD ($r^2 \geqq 0.6$) with a lead SNP. Loci were merged if they were separated by less than 250 kb. These distinct regions, containing all of these candidate SNPs, were considered to be a single independent genomic locus. All LD information was calculated from the 1000 Genomes Project reference panel [45]. Novel risk loci were defined as those not identified (separated by at least 250 kb) in the original GWAS samples used for these analyses [24, 25] and not identified as risk loci for ADHD or BD in previous studies.

Functional annotation

Positional and functional annotation of all candidate SNPs, in the genomic loci with a conjFDR value < 0.10 having an LD $r^2 \geqq 0.6$ with one of the independent significant SNPs, was performed using ANNOVAR [46], implemented in FUMA [44]. SNPs were also annotated with Combined Annotation Dependent Depletion (CADD) [47] scores, which predict how deleterious the SNP effect is on protein structure/function, RegulomeDB [48] scores, which predict the likelihood of

regulatory functionality, and chromatin states, which predict transcription/regulatory effects from chromatin states at the SNP locus [49, 50]. We also identified previously reported GWAS associations in the NHGRI-EBI catalog [51] overlapping with the identified loci. Finally, we queried SNPs for known expression quantitative trait loci (eQTLs) in the genotype tissue expression (GTEx) portal [52].

Evaluation of identified loci in an independent ADHD case-control cohort

To assess the robustness of the condFDR/conjFDR results we examined the most significant SNPs in the identified loci in the association summary statistics from a case-control ADHD cohort from deCODE Genetics (n = 10,217 cases, n = 338,344 controls). A description of this cohort is provided in the Supplementary Methods. In order to compare SNP effect directions, sign concordance was determined between the PGC ADHD GWAS [24] and deCODE cohorts.

Results

Genetic Overlap and Correlation

The conditional QQ plots suggest the presence of enrichment for ADHD given BD (Figure 1A), shown by the incremental incidence of association with ADHD (leftward deflection) as a function of the significance of association with BD. Similar and even more marked results are observed for the reverse relationship, BD conditioned on ADHD (Figure 1B). The LD score regression analysis is in line with the enrichment showing a positive genetic correlation between ADHD and BD (r_g 0.121, SE 0.038, p = 0.002).

We leveraged this cross-phenotype polygenic enrichment using condFDR analyses and re-ranked ADHD SNPs conditionally on their association with BD, and vice versa. At condFDR < 0.05 we identified 33 loci associated with ADHD after conditioning on BD (Supplementary Figure 1, Supplementary Table 1), 19 of which are novel ADHD-risk loci (Table 1). When considering the allelic effect direction for the 33 lead SNPs in these ADHD-risk loci, 23 have concordant direction of effect with BD (Supplementary Table 1). Functional annotation of the 19 novel ADHD-risk loci revealed that the majority are intergenic or intronic (Table 1). One lead SNP (rs992936, CADD = 20.5) has a CADD score above the threshold score of 12.37, suggestive of deleteriousness [47] (Supplementary Table 1). After querying the GTEx portal [52], five lead SNPs were identified as potential eQTLs for various tissues (Supplementary Table 2). Three were identified as eQTLs for genes within at least one brain region (Supplementary Table 2).

The inverse conditional analysis identified 94 loci associated with BD after conditioning on ADHD (Supplementary Figure 1, Supplementary Table 3), 40 of which are novel BD-risk loci (Table 2). When considering the allelic effect direction for the 94 lead SNPs in these BD-risk loci, 56 have concordant direction of effect with ADHD (Supplementary Table 3). Functional annotation revealed the majority of the 40 novel BD-risk loci to be intergenic or intronic (Table 2). Five lead SNPs were reported to have a CADD score greater than 12.37, suggestive of deleteriousness [47], and three lead SNPs reported low RDB scores (1f, 2a and 2b) indicative of regulatory functionality [48] (Supplementary Table 3). Querying the GTEx portal [52] for these novel BD-risk loci identified 12 lead SNPs as potential eQTLs for genes in at least one brain tissue (Supplementary Table 4). Further, 29 of the identified BD-risk loci overlap with lead SNPs from the analysis of bipolar I disorder only in the original GWAS (Supplementary Table 3) [25],

while none of the BD-risk loci overlap with lead SNPs from the analyses of bipolar II disorder or schizoaffective disorder–bipolar type (Supplementary Table 3) [25].

A total of five loci were jointly associated with ADHD and BD at conjFDR < 0.05 (Figure 2, Supplementary Table 5). Two of these loci (lead SNP rs323509, 5:103671867-104082179 and lead SNP rs11167721, 5:154772692-154984679) are novel risk loci for both ADHD and BD (Table 3), i.e. these loci were not identified in the original GWAS studies [24, 25] and not implicated in these disorders by previous studies. One shared locus (lead SNP rs11936939, 4:101463177-101593148) was novel for ADHD, but not BD. Two of these novel shared loci were included in the GWAS catalog due to reported associations with anorexia nervosa [53] and depression [54], and cognitive decline [55], respectively. Furthermore, all five shared loci have concordant effects on ADHD and BD risk (Supplementary Table 5), and none of these loci overlap with lead SNPs from the analyses of bipolar I disorder, bipolar II disorder or schizoaffective disorder–bipolar type (Supplementary Tables 3 and 5) [25].

Functional annotation of all SNPs with conjFDR < 0.1 within the loci shared between ADHD and BD revealed that all candidate SNPs (n=73) are intronic or intergenic (Supplementary Table 6). Of these 73 candidate SNPs, three SNPs (rs2431108, rs13162928, rs1956002) reported CADD scores above the 12.37 threshold score suggestive of deleteriousness [47]. After querying the GTEx portal [52], ten candidate SNPs, all within the same genomic locus, were identified as potential eQTLs for the *RP11-6N13.1* gene in the testis (Supplementary Table 7). Gene-set and pathway analysis, implemented in FUMA [44], of the genes nearest to these 73 lead SNPs

(Supplementary Table 6 revealed no significantly enriched biological processes, cellular components or molecular functions.

Evaluation of identified loci in an independent ADHD case-control cohort

Of the five loci shared between ADHD and BD (conjFDR < 0.05), lead SNPs within four of these loci showed concordant effect direction between the PGC GWAS and deCODE cohorts (Supplementary Table 5). Moreover, when considering all candidate SNPs within these five loci, 46/73 showed concordant direction of effect (Supplementary Table 6). For the ADHD-risk loci identified by conditioning on BD (condFDR < 0.01), 19/33 of the lead SNPs within these loci were concordant in the deCODE cohort (Supplementary Table 1). The concordance rates were similar for the ADHD-risk loci previously identified in the PGC ADHD GWAS [24] (7/12 concordant lead SNPs), and the additional ADHD-risk loci identified in the present study (12/21 concordant lead SNPs).

Discussion

The current study identified novel ADHD and BD associated risk loci, as well as novel genetic loci shared between these disorders, by applying the condFDR/conjFDR method to GWAS summary statistics [24, 25]. The results provide further evidence for a shared polygenic architecture between ADHD and BD, and therewith potential new insight into the molecular mechanisms that may explain the high comorbidity rates and shared phenotypes between these disorders [12, 13].

We observed cross-trait polygenic enrichment between ADHD and BD using conditional QQ plots (Figure 1), supporting recent genetic evidence [23] and prior epidemiological, neuroimaging and family studies [15]. This observed enrichment was supported by significant positive genome-wide genetic correlation identified in this study (r_g 0.121, SE 0.038, p = 0.002). Leveraging this enrichment, we used the condFDR approach to identify 19 novel risk loci for ADHD (Table 1) and 40 novel risk loci for BD (Table 2). Expanding on our condFDR results, we identified five risk loci shared by ADHD and BD using the conjFDR method (Table 3), two of which are novel risk loci for both disorders (lead SNP rs323509, 5:103671867-104082179 and lead SNP rs11167721, 5:154772692-154984679). Remarkably, when considering the identified genetic correlation, all of the lead and candidate SNPs within the five loci jointly associated with ADHD and BD show concordant direction of effect for these disorders (Supplementary Table 6). The identification of polygenic overlap between ADHD and BD, that includes agonistic SNP effects, may have important clinical implications. These results highlight a shared underlying genetic risk for ADHD and BD that remains to be fully characterized. Specific symptoms and/or clinical observations common to the diagnostic criteria for these disorders may have the same genetic causes, which may help to explain the high comorbidity rates [10, 12, 13] and difficulties in differential diagnosis between ADHD and BD [10, 11]. Although the shared genetic loci identified in this study all had concordant effect directions, and thus may not be useful for stratifying between ADHD and BD affected patients, they may aid the development of novel genetic prediction tools to identify patients at risk of comorbid ADHD and BD. Moreover, an improved understanding of the overlapping and discrete genetic components underlying these disorders may aid in the development of novel stratification tools to help reduce the difficulty in correctly diagnosing affected individuals.

To further evaluate the shared and ADHD-associated loci, identified utilizing the data from the PGC ADHD GWAS, we examined the lead and candidate SNPs in an independent ADHD case-control sample. Four of the five shared loci showed consistent direction of effect in the independent ADHD sample (Supplementary Table 5). In addition, the majority of candidate SNPs (46/73) within these shared loci showed similarly concordant effect direction, with similar concordance rates as described in the original PGC ADHD GWAS [24].

We identified 33 ADHD-associated risk loci after conditioning ADHD on BD. These include the 12 loci reported in the initial GWAS [24], two loci attributed to ADHD in previous studies (Supplementary Table 1) and 19 novel risk loci (Table 1). Similarly, after conditioning BD on ADHD, we identified 94 BD-associated risk loci. The original BD study reported 19 significant loci in a discovery phase GWAS (data we have used in this study) and 30 significant loci in a combined GWAS including the discovery and a replication sample. Amongst the BD-associated loci identified in this study (Supplementary Table 3), we replicated the 19 loci identified in the discovery phase of the original GWAS [25], as well as 15 loci only identified in the combined analysis [25]. In addition, we identified 21 loci attributed to BD in previous studies (Supplementary Table 3), and identify a further 40 novel BD-associated risk loci (Table 2). These results highlight how the condFDR approach can be used to exploit GWAS summary statistics for improved power for loci discovery.

Further analysis of the novel ADHD-associated risk loci suggests that six lead SNPs may function as eQTLs for a number of genes in numerous tissue types (Supplementary Table 2). Three of these SNPs (rs28535523, rs227280, rs6032660) were suggested to alter the expression

of nine genes in specific brain tissues, including the caudate basal ganglia, cerebellar hemisphere, cerebellum, cortex, frontal cortex BA9 and anterior cingulate cortex BA24. Among these differentially expressed genes, three (*CD40*, *MANBA*, *LRRC37A15P*) were recently identified as likely causal genes for ADHD [56], increasing confidence that these genes play some role in the etiology of the disorder. Both the *CD40* [57] and *MANBA* [58] genes encode proteins involved in the immune system providing further evidence for the hypothesis that dysfunction of the immune system may modulate risk of psychiatric disorders [59]. In addition, four of these genes (*GPX1*, *AMT*, *RNF123*, *INKA1*) are listed in the GWAS catalog for associations with general intelligence and educational attainment [51], two phenotypes linked with ADHD in epidemiological, clinical and genetic studies [37, 60–64], suggesting that these genes may play a role in brain networks involved in behavior and cognition.

A similar eQTL analysis of the lead SNPs for the novel BD-associated risk loci identified 28 SNPs that alter the expression of 68 genes in numerous tissue types (Supplementary Table 4). Of these, 12 SNPs were identified as eQTLs for 19 genes within 13 specific brain tissues (Supplementary Table 4). Three SNPs (rs11917269, rs2843728, rs4886883) were identified as eQTLs for the *HYAL3* (Cortex), *PLPP5* (Cerebellum) and *LINGO1* (Putamen) genes, respectively (Supplementary Table 4). These genes are indexed in the GWAS catalog for associations with schizophrenia and autism spectrum disorder, as well as general intelligence [51], highlighting their potential involvement in psychiatric and cognitive phenotypes. Interestingly, SNP rs4820214 was also identified as an eQTL for the *TOP3B* (Cortex, frontal cortex BA9, nucleus accumbens), *TOP3BP1* (Caudate, putamen, cerebellum, cortex, spinal cord

cervical c-1) and *PPM1F* (Putamen) genes, all of which were previously implicated with ADHD risk in the GWAS catalog [51].

One limitation of the condFDR/conjFDR approach is that it is sensitive to LD-biases intrinsic to the association p-values. The genetic variants with more correlations to their neighbours are more likely to tag any causal variants than more isolated variants and this could result in slightly inflated FDR estimates. Another limitation this method inherits from the GWAS it draws upon is that it is agnostic with regard to the specific causal variants underlying the overlapping genomic loci. These overlapping loci could result from both shared or separate causal variants, or "mediated pleiotropy", where one phenotype is causative of the other [65]. Further, since the cross-trait enrichment reflects the extent of polygenic overlap between the phenotypes as well as the power of the two GWAS samples analyzed, this enrichment will be more difficult to detect if the utilized GWAS samples are inadequately powered.

The current findings of shared genetic loci between ADHD and BD may suggest that there are overlapping clinical features between ADHD and BD, suggesting that subgroups of patients with mixed clinical features could benefit from specific interventions. In addition, it should be noted that there is a possibility that our findings of shared genetic loci between ADHD and BD may be the result of bias from misdiagnosis in the original GWAS studies [24, 25], i.e., that ADHD patients were misdiagnosed as BD, or vice versa. The number of such cases is estimated to be small due to the inclusion/exclusion criteria employed in these studies [24, 25], the low genetic correlation between these samples (r_g 0.121), and the low prevalence of the disorders. At any rate, this highlights the need for more meticulous phenotyping across psychiatric disorders in

future GWAS to more accurately determine the specific genetic architecture of these complex traits across current nosological categories [66, 67].

Moreover, another possible limitation to this study is the over-representation of BD1 (73%) in the BD GWAS, when compared to BD2 (17%) and SAB (5%) [25]. Although none of the shared loci between ADHD and BD overlapped with lead SNPs from the analyses of these BD-subtypes, a number of the identified BD-risk loci were shown to overlap with lead SNPs from the BD1 analysis (Supplementary Tables 3 and 5) [25]. This indicates a potential bias of the loci reported in this study to be more specific to BD1 and highlights the need to better clarify the genetic architecture of these BD-subtypes, when larger, well-powered samples become available. Finally, we show validation of the identified shared and ADHD-associated loci in an independent ADHD sample. Due to the smaller sample size of cases in this independent ADHD cohort, we were not able to perform true replication analyses using the condFDR/conjFDR method. An independent BD sample was not available for similar assessment. These results highlight the need to replicate the loci identified in this study in large well-powered independent cohorts and additional experimental work is needed in order to establish the functional implications of these loci and the reported tag SNPs.

In conclusion, we observed polygenic enrichment and identified five shared loci between ADHD and BD that may help to explain the underlying mechanisms behind the high rates of comorbidity observed for these disorders [12, 13, 15]. We leveraged this genetic overlap and identified 20 novel ADHD-risk loci and 53 novel BD-risk loci, and 4 loci associated with both disorders. These findings of shared polygenic architecture despite low genome-wide genetic

correlation have clinical implications, suggesting genetic factors underlying the comorbidity and overlapping phenotypes between ADHD and BD.

Acknowledgements

Funding: NIH (NS057198, EB00790); the Research Council of Norway (229129, 213837, 223273, 226971); the South-East Norway Regional Health Authority (2013-123); KG Jebsen Foundation (SKGJ-2011-36). The authors thank the Psychiatric Genetics Consortium (PGC) for access to GWAS data, and the many people who provided DNA samples. The authors thank Thomas Bjella, of the Oslo University Hospital & Institute of Clinical Medicine, for support with the database. The analyses were performed on resources provided by UNINETT Sigma2 - the National Infrastructure for High Performance Computing and Data Storage in Norway.

Conflicts of Interest

Dr. Andreassen has received a speaker's honorarium from Lundbeck and a consultant for HealthLytix Inc. Dr. Dale reports that he is a Founder of and holds equity in CorTechs Labs, Inc., and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc. He receives funding through research grants from GE Healthcare to UCSD. The terms of these arrangements have been reviewed by and approved by UCSD in accordance with its conflict of interest policies. G.B.W., O.O.G., H.S. and K.S. are employees of deCODE genetics/Amgen. The other authors have no conflicts of interest to declare.

Supplementary information is available at MP's website

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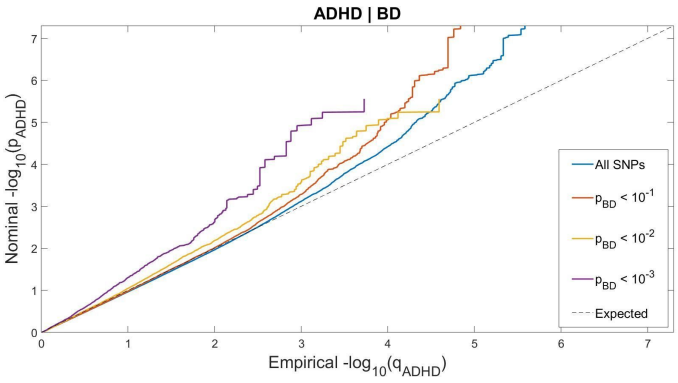
Figure Legends

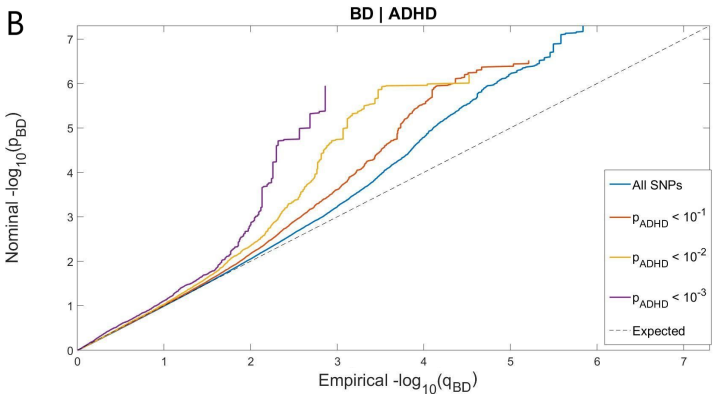
Figure 1. Conditional QQ plots showing cross-phenotype polygenic enrichment between attention deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD). Plotted are the nominal vs empirical −log10 p-values (corrected for inflation) for the trait of interest, below the standard genome-wide association study threshold of $p < 5.0 \times 10^{-8}$, as a function of significance of association with the conditional trait at the level of $p \leq 0.10$, $p \leq 0.01$ and $p \leq 0.001$. The dashed lines indicate the null hypothesis. (A) ADHD is the trait of interest and is conditioned on BD. (B) BD is the trait of interest and is conditioned on ADHD.

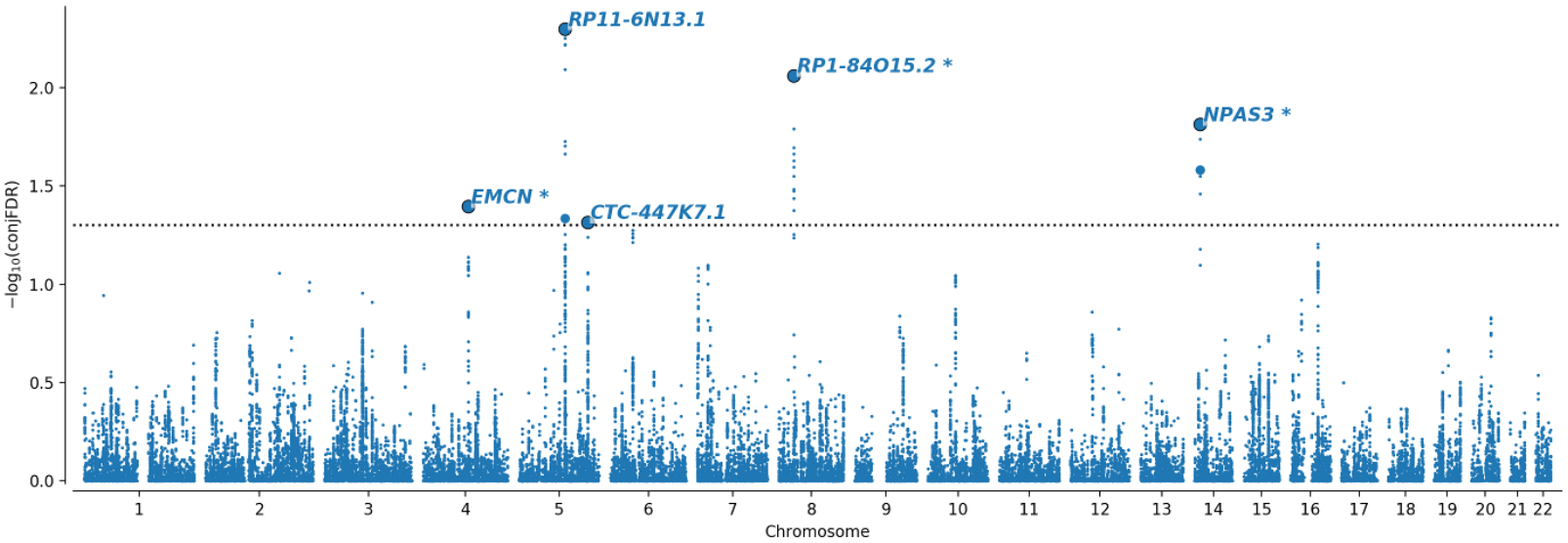
Figure 2. Common genetic variants jointly associated with attention deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) at conjunctional false discovery rate (conjFDR) < 0.05. Manhattan plot showing the –log10 transformed conjFDR values for each SNP on the y-axis and chromosomal positions along the x-axis. The dotted horizontal line represents the threshold for significant shared associations (conjFDR < 0.05). Independent lead SNPs are encircled in black, and are annotated to the nearest gene. Further details for these shared loci are provided in Supplementary Table 5 and 7. * Loci previously identified for ADHD [24, 68] and/or BD [69–72].

A


ADHD | BD
Nominal -log10(pADHD)
Empirical -log10(qADHD)
All SNPs
pBD < 10-1
pBD < 10-2
pBD < 10-3
Expected

B


BD | ADHD
Nominal -log10(pBD)
Empirical -log10(qBD)
All SNPs
pADHD < 10-1
pADHD < 10-2
pADHD < 10-3
Expected


RP11-6N13.1
RP1-84O15.2 *
NPAS3 *
EMCN *
CTC-447K7.1
2.0
1.5
1.0
0.5
0.0
−log10(conjFDR)
1
2
3
4
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Chromosome

Table 1. Novel genomic loci associated with attention deficit/hyperactivity disorder (ADHD) at conditional FDR (condFDR) < 0.05 given association with bipolar disorder (BD).

Locus	Chr	Lead SNP	A1/A2	Nearest Gene	Functional category	P-value ADHD	Odds Ratio ADHD	P-value BD	Odds ratio BD	condFDR
3	1	rs2391769	A/G	*EEF1A1P11*	intergenic	1.038E-07	0.928	2.923E-01	0.985	1.972E-02
6	3	rs28535523	C/T	*UBA7*	intronic	8.248E-06	1.079	2.750E-03	1.053	2.564E-02
8	4	rs1484144	T/C	*LINC01088:NAA11*	ncRNA_intronic	1.984E-06	1.066	7.564E-03	1.037	1.664E-02
9	4	rs11936939	C/T	*EMCN*	intergenic	1.371E-05	0.941	1.193E-04	0.948	1.302E-02
10	4	rs227280	A/G	*MANBA*	intronic	7.050E-08	0.924	6.491E-01	1.007	2.650E-02
12	5	rs12658032	A/G	*RP11-6N13.1*	ncRNA_intronic	1.154E-07	1.078	2.685E-04	1.053	2.340E-04
13	5	rs11167721	C/T	*CTC-447K7.1*	intergenic	8.348E-05	1.063	9.093E-05	1.062	4.832E-02
14	6	rs141547796	G/A	*RP1-28O17.1*	intergenic	9.640E-08	0.872	6.753E-01	1.011	3.297E-02
17	7	rs2218378	A/G	*CADPS2*	intronic	2.048E-07	0.929	6.246E-01	0.993	4.860E-02
19	8	rs72673548	T/C	*RP11-700E23.3*	intergenic	1.163E-06	0.891	2.149E-02	0.946	2.112E-02
20	10	rs713240	C/T	*ARID5B*	intronic	3.357E-06	1.065	2.080E-02	0.969	4.178E-02
22	11	rs10835362	G/A	*RP11-960D24.1*	intergenic	5.379E-07	0.933	4.501E-02	0.973	1.902E-02
24	14	rs4981170	A/G	*NPAS3*	intronic	1.298E-05	0.925	9.819E-05	0.933	1.245E-02
26	15	rs60798171	T/G	*RP11-138H10.2*	intergenic	7.250E-07	0.925	4.300E-02	0.968	2.275E-02
28	16	rs1436380	A/G	*CDH8*	intronic	3.710E-06	0.938	2.257E-04	0.951	4.531E-03
30	18	rs4144756	G/A	*RP11-188I24.1*	intergenic	1.455E-07	1.080	5.966E-01	1.008	3.858E-02
31	18	rs17084232	C/T	*RP11-47G4.2*	intergenic	1.703E-07	1.195	2.531E-01	0.961	2.476E-02
32	20	rs6032660	G/A	*RPL13P2*	intergenic	1.361E-05	0.934	8.940E-04	0.950	2.006E-02
33	21	rs992936	T/C	*NEK4P1*	intergenic	1.783E-07	1.074	2.716E-01	1.015	2.658E-02

The most strongly associated SNPs in novel genomic loci associated with ADHD at condFDR<0.05 given association with BD after merging regions < 250 kb apart into a single locus. The table presents chromosomal position (Chr), nearest gene and functional category, as well as p-values and effect sizes (odds ratios) from the original summary statistics on ADHD [26] and BD [27]. The effect sizes are given with reference to allele 2 (A2). For more details and the full list of all loci associated with ADHD at condFDR<0.05, see Supplementary Table 1.

Table 2. Novel genomic loci associated with bipolar disorder (BD) at conditional FDR (condFDR) < 0.05 given association with attention deficit/hyperactivity disorder (ADHD).

Locus	Chr	Lead SNP	A1/A2	Nearest Gene	Functional category	P-value BD	Odds Ratio BD	P-value ADHD	Odds ratio ADHD	condFDR
1	1	rs1278516	G/A	*RP5-850O15.4*	intergenic	5.558E-07	0.893	2.745E-02	1.049	8.622E-03
3	1	rs12563424	T/C	*TMEM56*	intergenic	5.293E-07	0.933	9.061E-02	0.977	1.796E-02
5	1	rs80148877	T/C	*RP4-640E24.1*	intergenic	1.092E-06	0.860	1.495E-01	1.045	3.618E-02
6	1	rs4652746	G/A	*AL513344.1*	intergenic	1.458E-06	1.096	8.772E-02	1.034	3.168E-02
7	1	rs7550853	A/C	*SMYD3*	intronic	1.499E-05	0.936	1.176E-02	0.962	4.128E-02
8	2	rs5015511	G/A	*AC068490.2*	ncRNA_intronic	1.122E-04	1.054	1.095E-04	1.057	3.928E-02
14	2	rs12621381	A/C	*snoU13*	intergenic	9.798E-07	0.934	4.141E-03	0.962	3.756E-03
18	3	rs11917269	G/T	*CACNA2D2*	intronic	1.322E-06	0.926	8.249E-03	0.958	7.084E-03
20	3	rs3774608	G/A	*CACNA1D*	intronic	7.716E-06	0.940	1.068E-02	1.036	2.604E-02
21	3	rs62252499	A/G	*CADM2*	intronic	7.247E-05	1.063	1.557E-03	1.045	4.577E-02
23	3	rs6767302	A/G	*HMGN2P25*	downstream	2.123E-07	1.073	4.113E-01	1.011	2.796E-02
24	3	rs55657715	A/G	*ATP11B*	intronic	6.111E-05	0.945	1.254E-03	1.047	3.741E-02
26	4	rs6829845	A/G	*IL21*	intergenic	2.940E-07	1.076	9.240E-03	0.964	2.756E-03
30	5	rs7707252	A/G	*Y_RNA*	intergenic	2.987E-05	0.940	3.143E-04	1.056	1.386E-02
32	5	rs323509	A/C	*RP11-6N13.1*	ncRNA_intronic	8.940E-06	1.067	1.655E-06	1.073	5.345E-03
35	5	rs9324815	A/G	*CTC-447K7.1*	downstream	2.516E-05	0.942	3.118E-04	0.950	1.214E-02
42	7	rs6947663	G/A	*AC007652.1*	ncRNA_intronic	3.947E-05	0.943	4.002E-03	1.043	4.494E-02
43	7	rs12538191	G/A	*RP4-647J21.1*	intergenic	1.461E-07	0.909	9.158E-02	1.033	8.453E-03
45	7	rs73147614	G/A	*SMURF1*	intronic	3.544E-05	0.838	4.694E-03	1.108	4.515E-02
50	8	rs2843728	C/T	*RP11-90P5.2*	ncRNA_intronic	2.918E-06	0.934	1.272E-02	0.965	1.545E-02
51	8	rs10505139	A/G	*RP11-403P13.1*	intergenic	6.337E-07	0.915	1.940E-01	0.977	3.115E-02
52	8	rs57957974	C/A	*PARP10*	intronic	4.977E-07	1.076	2.120E-01	1.018	2.881E-02
53	9	rs57298275	T/C	*ANP32B*	intronic	3.392E-05	1.060	7.689E-04	1.047	1.993E-02
54	9	rs113314512	G/A	*RP11-6F6.1*	intergenic	3.268E-05	1.174	3.734E-03	1.133	3.871E-02
55	9	rs10120508	G/A	*RP11-295D22.1*	intergenic	9.078E-07	0.930	2.475E-01	1.018	4.293E-02
56	10	rs7915021	C/T	*ST8SIA6*	intronic	6.859E-07	0.906	9.293E-02	0.967	2.119E-02
68	12	rs17680262	C/T	*TCHP*	UTR3	6.714E-06	1.115	2.196E-02	0.945	3.553E-02
69	14	rs72673100	C/A	*LINC00641*	ncRNA_exonic	1.769E-06	0.931	1.134E-01	0.974	4.068E-02
74	15	rs4886883	A/G	*RP11-307C19.2*	ncRNA_intronic	1.604E-05	0.942	5.222E-03	1.040	2.862E-02
77	16	rs58867145	C/T	*RP11-266L9.5*	intergenic	2.192E-05	1.073	1.087E-03	1.059	1.676E-02
78	16	rs976498	C/T	*RP11-439I14.2*	intergenic	6.602E-07	1.098	1.721E-01	1.025	2.971E-02
79	16	rs10492859	A/G	*CDH13:RP11-22H5.2*	ncRNA_intronic	4.454E-06	1.076	4.385E-02	1.033	4.101E-02
80	17	rs2302776	A/G	*MED24*	intronic	9.222E-07	1.070	2.283E-01	1.017	4.144E-02
81	17	rs7217151	C/T	*UTP18*	intronic	4.378E-07	1.071	3.532E-01	1.013	3.618E-02
84	19	rs3843751	C/T	*SLC44A2*	intronic	1.602E-07	1.079	1.996E-01	0.981	1.508E-02
86	19	rs56332086	C/T	*ZNF584*	ncRNA_exonic	2.753E-05	0.930	7.121E-03	0.957	4.668E-02
90	20	rs12624433	G/A	*SLC12A5*	intronic	7.448E-05	1.063	1.056E-03	1.052	4.036E-02

91	20	rs1850	T/C	*RP5-955M13.4:KCNG1*	ncRNA_intronic	1.490E-07	0.927	6.569E-01	1.006	3.202E-02
92	20	rs6090435	G/A	*RP4-697K14.3*	upstream	4.393E-07	0.927	4.019E-01	0.988	3.907E-02
93	22	rs4820214	C/T	*KB-1027C11.4*	intergenic	6.717E-07	0.935	1.154E-01	0.978	2.383E-02

The most strongly associated SNPs in novel genomic loci associated with BD at condFDR<0.05 given association with ADHD after merging regions < 250 kb apart into a single locus. The table presents chromosomal position (Chr), nearest gene and functional category, as well as p-values and effect sizes (odds ratios) from the original summary statistics on BD [27] and ADHD [26]. The effect sizes are given with reference to allele 2 (A2). For more details and the full list of all loci associated with BD at condFDR<0.05, see Supplementary Table 3.

Table 3. Novel loci jointly associated with attention deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) at conjunctional FDR<0.05.

Locus	Chr	Lead SNP	A1/A2	Nearest Gene	Functional category	P-value ADHD	Odds Ratio ADHD	P-value BD	Odds ratio BD	conjFDR
1	4	rs11936939	C/T	*EMCN**	intergenic	1.371E-05	0.941	1.193E-04	0.948	4.023E-02
2	5	rs323509	A/C	*RP11-6N13.1*	ncRNA_intronic	1.655E-06	1.073	8.940E-06	1.067	5.027E-03
3	5	rs11167721	C/T	*CTC-447K7.1*	intergenic	8.348E-05	1.063	9.093E-05	1.062	4.832E-02

The most strongly associated SNPs in independent genomic loci shared between ADHD and BD at conjFDR<0.05 after merging regions < 250 kb apart into a single locus. The table presents chromosomal position (Chr), nearest gene and functional category, as well as p-values and effect sizes (odds ratios) from the original summary statistics on ADHD [26] and BD [27]. The effect sizes are given with reference to allele 2 (A2). For more details and a list of all candidate variants in these loci, see Supplementary Table 6 and 7. * Novel for ADHD only.