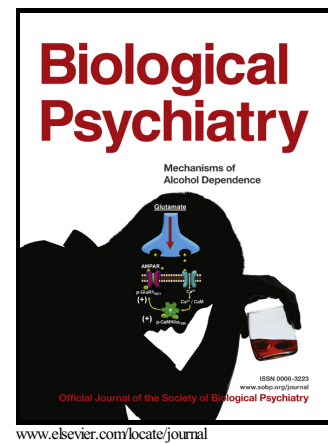


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Meta-analysis of ADHD and BPD GWAS

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Genetic overlap between Attention-Deficit/Hyperactivity Disorder and Bipolar Disorder:

Evidence from GWAS meta-analysis.

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Short title: Meta-analysis of ADHD and BPD GWAS

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) would be particularly likely to show genetic covariation with ADHD.

Methods: GWAS data were available for 4,609 individuals with ADHD, 9,650 individuals with BPD (5,167 thereof with early-onset BPD) and 21,363 typically developing controls. We conducted a cross-disorder GWAS meta-analysis to identify whether the observed comorbidity between ADHD and BPD could be due to shared genetic risks.

Results: We found a significant SNP-based genetic correlation between ADHD and BPD in the full and age-restricted samples ($r_{\text{Full}} = 0.64$, $p = 3.13 \times 10^{-14}$; $r_{\text{Restricted}} = 0.71$, $p = 4.09 \times 10^{-16}$). 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 eQTLs with putative functional consequences for *NT5DC1*, *NT5DC2* and *CACNB3* expression, while functional predictions implicated *ABLIM1* as an allele-specifically expressed gene in neuronal tissue.

Conclusions: The SNP-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.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most frequent neuropsychiatric disorder in childhood and frequently persists into adulthood. Bipolar disorder (BPD) is amongst 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 co-presents 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, are not increased in BPD. This failure to find a shared genetic signal may be due to prior studies' lack of statistical power, and the limited set of polymorphisms examined. To address these shortcomings, a genome-wide cross-disorder meta-analysis of BPD and ADHD was conducted in a large sample of individuals with BPD, with ADHD and typically developing controls from the Psychiatric Genomics Consortium. Because ADHD is a childhood onset disorder (prior to 12 years), we hypothesized that the overlap would be most obvious in BPD cases with a relatively early onset (age of onset ≤ 21 years), as this group could be assumed to have a more neuro-developmental etiology (8). Restricting the age range of the sample to those with an onset ≤ 21 years may also increase the power for gene-finding since 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 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 PGC 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 the **Supplemental Tables S1a** and **S1b**. The ADHD sample comprised 4,609 cases and 8,519 controls. The full BPD sample comprised 9,650 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 5,167 (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 score regression (LDSR) was used to estimate the SNP-based genetic correlation (r_G) between ADHD and both BPD samples. For LDSR, each data set underwent additional filtering. Only markers overlapping with HapMap Project Phase 3 SNPs and passing the following filters were included: INFO score > 0.9 , study missingness of 0 and MAF $> 1\%$ (where available). Indels and strand-ambiguous SNPs were removed.

The analysis was conducted using a two-step procedure with the LD-scoring analysis package (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). These GWAS 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, 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 to 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 miRNA 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-seq 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 (TFBS) were predicted with the web-based tool MatInspector version 2.1 (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 bp 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 as compared to the full sample ($r_{G\text{full}} = 0.64$, $SE = 0.02$, $p = 3.13 \times 10^{-14}$; $r_{G\text{restricted}} = 0.71$, $SE = 0.02$, $p = 4.09 \times 10^{-16}$; **Table 1**).

Full sample

Figure 1A shows the Manhattan plot of the primary cross-disorder meta-analysis and **Figure S1A** shows the corresponding QQ plot. Two independent loci, located on chromosomes 6 and 10, reached genome-wide significance ($p < 5 \times 10^{-8}$). The strongest signal ($p = 2.47 \times 10^{-8}$) was for SNP rs7089973, located on chromosome 10 in an intronic region of the TAF9B RNA polymerase II, TATA box binding protein (TBP)-associated factor, 31kDa pseudogene 2 gene (*TAF9BP2*; **Figure 2A**) which is a pseudogene of yet unknown function. SNP rs7089973 is in linkage disequilibrium (LD) with SNPs in the TruB Pseudouridine (Psi) Synthase Homolog 1 gene (*TRUB1*; best $p = 8.89 \times 10^{-6}$) and with the family with sequence similarity 160 member B1 gene (*FAM160B1*; best $p = 5.45 \times 10^{-8}$).

On chromosome 6, the strongest signal was for SNP rs11756438, located in an intronic region of the centrosomal protein 85kDa-like gene (*CEP85L*; $p = 4.36 \times 10^{-8}$; **Figure 2B**) encoding a protein of unknown function. Furthermore, rs11756438 is in LD with SNPs in the Bromodomain Containing 7 Pseudogene 3 gene (*BRD7P3*; best $p = 9.39 \times 10^{-7}$), the phospholamban gene (*PLN*; best $p = 7.25 \times 10^{-7}$), and the Solute Carrier Family 35, Member F1 gene (*SLC35F1*; best $p = 1.00 \times 10^{-5}$). Both associated regions showed the same direction of effect in ADHD and BPD. The disorder-specific contribution to each genome-wide significant locus can be found in **Table 2**, and forest plots from individual GWAS are shown in **Figure S5**. Top-ranked SNPs for this analysis ($p < 10^{-6}$) are summarized in **Table S3**.

Age-Restricted BPD sample

The Manhattan plot for the age-restricted analysis is shown in **Figure 1B**; the respective QQ plot is provided in **Figure S1B**. One SNP on chromosome 5 reached genome-wide significance; forest plots of results from individual GWAS are shown in **Figure S5**. The strongest signal ($p = 2.47 \times 10^{-8}$) was observed for SNP rs58502974, located in an intron of the Adenylate Cyclase 2 (Brain) (*ADCY2*)

gene (**Figure 2C**). The product of this gene is a member of the family of adenylate cyclases, which are membrane-associated enzymes that catalyze the formation of the secondary messenger cyclic adenosine monophosphate (cAMP). Top-ranked SNPs for this analysis ($p < 10^{-4}$) are summarized in **Table S3**.

Allele-specific transcriptional activity

None of the top-100 associated SNPs in the primary and restricted analyses (**Supplemental Table S3**) were listed in the Geuvadis database of cis-eQTLs defined in lymphoblastoid cell lines that were mainly derived from the 1000 Genomes sample (18). To estimate the potential eQTL function in other tissues, direct bioinformatics prediction was thus used and found differential binding of transcription factors for 13 markers in the primary and four in the restricted GWAS, which involved neuro-relevant transcription factors at seven and one sites, respectively (**Supplemental Table S5**). A notable finding among those was for the gene *ABLIM1*. Allele-specific binding sites of miRNAs at the 3'-UTR of family with sequence similarity 160, member B1 (*FAM160B1*) transcripts were also observed (**Supplemental Table S5**).

Extending this analysis to evaluate top-ranked SNPs ($p < 10^{-4}$) for effects on transcriptional activity, we queried the Geuvadis database (18) for known eQTLs. Of the 4,806 SNPs displaying a trend towards association ($p < 1 \times 10^{-4}$) in one of the two analyses, 192 indeed were known eQTLs (**Supplemental Table S4**). Of those, 74 markers influenced the expression of 5'-nucleotidase domain containing 2 (*NT5DC2*); the expression of its homolog *NT5DC1* was modulated by 17 SNPs. Two SNPs were found to influence the expression of the calcium channel, voltage-dependent, beta 3 subunit (*CACNB3*). The accumulation of eQTLs at the *NT5DC* loci especially may be explained by LD. Indeed, when we tested the total number of eQTLs, it did not exceed expectation in either the full or the restricted analysis ($OR_{\text{primary}}=0.91$, $p_{\text{primary}}=0.27$; $OR_{\text{restricted}}=0.97$, $p_{\text{restricted}}=0.84$).

Discussion

In this study, we set out to identify shared genetic risk factor for ADHD and BPD through cross-disorder meta-analysis of the existing GWAS samples from the Psychiatric Genomics Consortium. We hypothesized that overlap between the disorders might be most pronounced in BPD cases with an early age of onset, and that restricting the analysis to samples with an onset ≤ 21 would increase the power of gene-finding by reducing heterogeneity (8). Our findings clearly show the substantial and significant genetic correlation between ADHD and BPD which supports the existence of genome-wide significant, shared genetic risk variants for ADHD and BPD ($r_{\text{Full}} = 0.64$, $SE = 0.08$, $p = 3.13 \times 10^{-14}$; $r_{\text{Restricted}} = 0.71$, $SE = 0.09$, $p = 4.09 \times 10^{-16}$; **Table 1**). We contrasted these results by estimating the genetic correlation between ADHD and BPD using previously published data sets and found the same correlation pattern (Supplemental Table S2).

In the full sample, we found two genome-wide significant loci and 10 with suggestive evidence of association ($p < 10^{-6}$; **Supplemental Table S3**). Although the statistical power was potentially lower in the age-restricted sample, one significant finding was observed. The region identified was different from the top-findings in the primary analysis, raising the possibility of development-specific gene activity in these two conditions. When specifically considering the BPD analyses (Table S3, also compare Figure S2A with S2B), it becomes clear that almost all top cross-disorder SNPs have lower p values in the age-restricted BPD sample as compared to the full BPD sample, despite its lower power. This might point to a stronger genetic component of early-onset BPD and consequently a different etiology as compared to late-onset BPD (20). However, these findings are still preliminary addressing this issue was not the major aim of our analysis and further work is clearly needed to adequately answer such questions.

Our top hit in the full analysis was present on chromosome 10 in the gene *TAF9BP2*. This being a pseudogene of unknown function, we cannot speculate about its potential involvement in the ADHD-BPD covariation. *TRUB1*, which includes variants in LD with the top SNP may constitute a potential candidate gene; its product is a member of the pseudouridine synthase gene family and may function as RNA chaperone, altering aspects of mRNA metabolism known to be affected by RNA structure (21). The protein encoded by *CEP85L*, suggested to be involved by the hit on chromosome 6,

was identified as a breast cancer antigen (22); the gene was also associated in a meta-analysis with the myocardial repolarization (23, 24), the latter lending some support to the notion that the gene's product is involved in neural conduction. This is the first time that genes in these loci are associated with psychiatric diseases, so the mechanisms by which variants in those might affect disease risk remain elusive. Our eQTL analyses did not provide evidence for a direct effect of the variation on the expression of the implicated genes or surrounding genes in LD with the hits. Furthermore, the functions of these genes are not well described, highlighting the need for further research.

The best hit found in the age-restricted sample is more obviously functionally significant. *ADCY2*, which codes for adenylate cyclase 2, is a key regulator of cyclic AMP metabolism and thus of second messaging by activating PKA, thereby triggering CREB phosphorylation (25). Both the PKA and CREB pathways (26, 27) have been implicated in BPD, and *CREB1* is a well-documented candidate gene for BPD (28). Recently, a SNP in *ADCY2* was also found to be genome-wide significantly associated with BPD (29). There is a vast literature on disturbances of serotonin and dopamine signaling in ADHD; both monoamines target G-protein coupled receptors (GPCRs) that use *ADCY2* in their signal transduction cascades, so it is conceivable that this protein is also relevant to ADHD. As this association became significant ($p=4.5\times 10^{-8}$) when restricting the BPD sample to an age of onset ≤ 21 years, the signal likely may be associated with a more neuro-developmental form of BPD. One hypothesis for future research is that adenylate cyclase signaling is a core mechanism mediating the comorbidity between ADHD and BPD.

Our primary meta-analysis yielded 10 suggestive loci ($p < 10^{-6}$). In addition to the aforementioned genes, these loci comprise the following candidate genes, each supported by at least three suggestive associations: On chromosome 1, we observed a suggestive association with the retinoid X receptor, gamma gene (*RXRG*). *RXRG* codes for retinoid receptor gamma - a regulator of dopamine signaling, cocaine response, and affective behaviors in mice (30, 31). This makes it an attractive candidate for both BPD and ADHD. The gene has been suggested to have an effect on hippocampal volume by QTL analysis in mice (32) and has been associated with sensation seeking (33), a personality trait associated with combined-type ADHD (34). On chromosome 3, a signal for the

neurologin 1 (*NLG1*) gene was also found. The neurologin protein family has already been implicated in a wide range of neuropsychiatric disorders including autism, schizophrenia, and BPD (35).

Presence of eQTLs was evaluated in SNPs with association p-values $<10^{-4}$ in either of the cross-disorder GWAS meta-analyses (**Supplemental Table S5**). Several interesting candidate genes for ADHD-BPD covariation were found to be regulated by multiple SNPs in our list serving as eQTLs. Of greatest interest are the findings implicating two members of the NT5DC family, a family of haloacid dehalogenase (HAD)-type phosphatases (36). *NT5DC1* has been associated with BPD in several studies, showing the strongest association with the disorder in NIMH Genetics Initiative bipolar pedigrees (37). Importantly, we recently observed an association between rare variants in this gene and adult ADHD (under review). *NT5DC2* has previously been found associated with schizophrenia; furthermore, *NT5DC2* is a target of miR-137 and is differentially methylated as a function of childhood maltreatment in BPD patients (38). Another interesting finding was for *CACNB3*, which codes for a voltage-gated calcium channel involved in neuronal morphology and differentiation; its transcript is targeted by miR-34a, which is upregulated in cerebellum of bipolar patients (39). Allelic variation in *ABLIM1*, which has previously been associated with novelty seeking, harm avoidance, reward and alcohol dependence (40), also appears to be a plausible finding.

Our finding that putative promoter regions containing the top-ranked associated SNPs do not contain known eQTLs was against our predictions of allele-specific effects on transcription. This discordance may, on the one hand, be attributed to the known high false positive rate of pattern searches with position-specific scoring matrices (19). On the other hand, the eQTL dataset was derived from analyses of lymphoblastoid cell lines (18), and it is therefore conceivable that the allele-specific transcription factor binding sites may serve as functional eQTLs in a different tissue context.

The findings described here need to be interpreted in the light of several caveats: The differential diagnosis especially between BPD and adult ADHD can be challenging. While this does not affect the ADHD sample, which was ascertained in childhood, it might pose a problem for the BPD sample: some shared signals might be due to patients with adult ADHD having falsely received a diagnosis of BPD. Given that all studies included here relied on DSM inclusion criteria, we are confident that misdiagnosis is at least not common enough to account for genome-wide significant

hits. Ethnic heterogeneity might influence the results as well, although we aimed to control for this by including MDS components in every GWAS included in the meta-analyses. Finally, sample sizes in our cross-disorder analyses were still rather small for complex genetic traits. This was particularly damaging in the restricted analysis, where the reduction in sample size masked the potential increase in power due to the reduction in etiological heterogeneity (discussed above).

In conclusion, we provide evidence for the genetic overlap between ADHD and BPD. This genome-wide SNP-based genetic overlap confirms the involvement of pathways such as G-protein-coupled signaling already known for their role in hyperactivity and/or emotional behaviors, and implicate a new candidate pathway (i.e. mRNA stability) in the pathophysiology of both ADHD and BPD.

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Figure Legends

Figure 1. Manhattan plot of the primary (a) and restricted (b) cross-disorder meta-analyses. Only SNPs with p values ≤ 0.05 are shown; Horizontal lines show threshold for genome-wide significance ($p < 5 \times 10^{-8}$ in red) and suggestive association ($p < 1 \times 10^{-6}$ in blue).

Figure 2A. Regional plot for genome-wide significant locus on chromosome 10 for the primary meta-analysis.

Figure 2B. Regional plot for genome-wide significant locus on chromosome 6 for the primary meta-analysis.

Figure 2C. Regional plot for genome-wide significant locus on chromosome 5 for the restricted meta-analysis.

Results for **Figure 2** are shown as $-\log(p\text{-value})$ for genotyped and imputed SNPs. The SNP showing strongest association is shown in the purple circle. The color of the remaining markers reflects r^2 of the strongest associated SNP. The recombination rate is plotted in blue.

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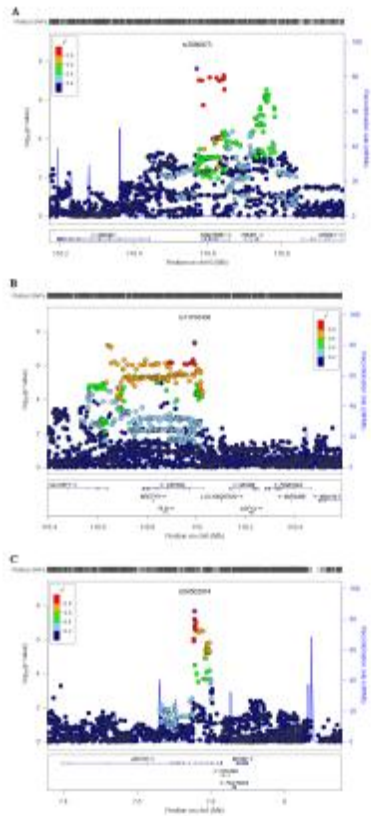
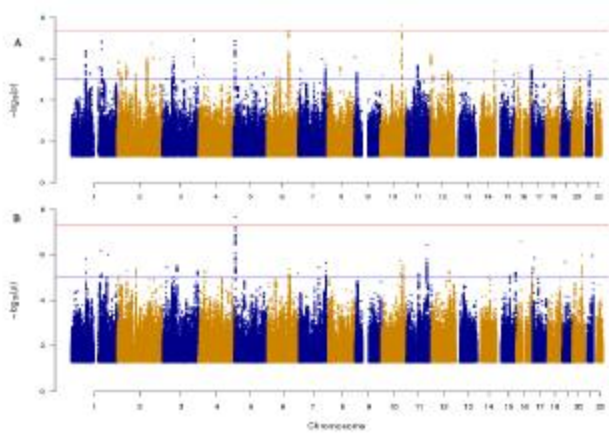
Table 1: Results from the univariate heritability analysis (h^2g [SE]), and genetic correlation between data from ADHD and BPD complete and age restricted samples.

BPD cohort	N (cases/controls)	Heritability	SE	Genetic correlation with ADHD	SE	Z-score	P-value
Age restricted	5,167/12,844	0.119	0.023	0.7062	0.087	7.593	4.09×10^{-16}
Full sample	9,650/12,844	0.068	0.024	0.6392	0.084	8.136	3.13×10^{-14}

ADHD: $N_{\text{cases}}=4,609$ and $N_{\text{controls}}=8,519$, SNP-based h^2 (observed)= 0.0652 (SE=0.0279)**Table 2.** Association results showing effect size and p for genome-wide significant loci by disorder for the primary and restricted meta-analyses.

Primary Meta-Analysis												
SNP	Location (bp:chr)	A1/A2	M AF	OR _A _{DHD}	P _{ADHD} _D	SE _A _{DHD}	OR _{BPD}	P _{BPD}	SE _B _{PD}	OR _{MA}	P _{MA}	Gene
rs7089973	10:11656	A/C	0.3	0.90	1.56×10^{-3}	0.03	0.90	4.39×10^{-6}	0.0	0.9	2.47×10^{-8}	TAF9
	9565		6									
rs11756438	6:	A/C	0.3	1.11	6.14×10^{-4}	0.03	1.11	1.85×10^{-5}	0.0	1.1	4.36×10^{-8}	CEP8
	1189936		4									
32												
Age Restricted Meta-Analysis												
SNP	Location (bp:chr)	A1/A2	M AF	OR _A _{DHD}	P _{ADHD} _D	SE _A _{DHD}	OR _{BPD}	P _{BPD}	SE _B _{PD}	OR _{MA}	P _{MA}	Gene
rs58502974	5: 7755900	A/T	0.4	1.14	1.84×10^{-5}	0.03	1.11	2.33×10^{-4}	0.0	1.1	2.11×10^{-8}	ADCY2

bp=base pairs; Chr= chromosome; MAF=minor allele frequency; OR=odds ratio; P=p value; SE=standard=standard error of the OR; ADHD=Attention-Deficit/Hyperactivity Disorder; BPD=Bipolar Disorder.



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