

Risk variants and polygenic architecture of disruptive behavior disorders in the context of attention-deficit/hyperactivity disorder

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Attention-Deficit/Hyperactivity Disorder (ADHD) is a childhood psychiatric disorder often comorbid with disruptive behavior disorders (DBDs). Here, we report a GWAS meta-analysis of ADHD comorbid with DBDs (ADHD + DBDs) including 3802 cases and 31,305 controls. We identify three genome-wide significant loci on chromosomes 1, 7, and 11. A meta-analysis including a Chinese cohort supports that the locus on chromosome 11 is a strong risk locus for ADHD + DBDs across European and Chinese ancestries ($rs7118422$, $P = 3.15 \times 10^{-10}$, $OR = 1.17$). We find a higher SNP heritability for ADHD + DBDs ($h^2_{SNP} = 0.34$) when compared to ADHD without DBDs ($h^2_{SNP} = 0.20$), high genetic correlations between ADHD + DBDs and aggressive ($r_g = 0.81$) and anti-social behaviors ($r_g = 0.82$), and an increased burden (polygenic score) of variants associated with ADHD and aggression in ADHD + DBDs compared to ADHD without DBDs. Our results suggest an increased load of common risk variants in ADHD + DBDs compared to ADHD without DBDs, which in part can be explained by variants associated with aggressive behavior.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common childhood onset behavioral disorder affecting around 5% of children and 2.5% of adults¹. Comorbidity with other psychiatric disorders is common among children with ADHD, and disruptive behavior disorders (DBDs) are the most frequently co-occurring conditions². DBDs comprise oppositional defiant disorder and conduct disorder. Both have a childhood onset and are characterized by persistent patterns of oppositional, defiant, disobedient and disruptive behavior and antisocial rule-breaking, and aggressive behaviors such as being destructive, physically cruel towards others, and rule violations³. DBDs have a prevalence of 3–10%^{4,5} among children and, are around twice as frequent in males compared to females⁶ and DBDs are associated with a 3-fold increased risk of premature death⁷, with higher mortality rates than in ADHD⁸. Different comorbidity rates of ADHD with DBDs have been reported, some studies have found that approximately 30–40% of children with ADHD have comorbid DBDs (ADHD + DBDs)^{9–11}, while a study of 1.92 million individuals from Denmark found that 17% of those with ADHD were also diagnosed with DBDs⁸. Among those with DBDs in the same Danish cohort, more than half (57%) had a comorbid diagnosis of ADHD⁷. ADHD in combination with diagnosed DBDs or excessive aggressive and disruptive behaviors increases the risk for several detrimental outcomes in individuals with ADHD including increased risks for substance use disorders^{12–14}, in-patient psychiatric admission¹⁵, transgression^{16,17}, risky behavior¹⁸, and premature death compared to those diagnosed with ADHD only⁸.

Both genetic and environmental factors influence the risk for ADHD and DBDs with twin heritability estimates of 0.74¹⁹ and 0.40–0.70^{20–22}, respectively. Twin studies have also suggested that ADHD + DBDs is a more severe and genetically loaded subtype of ADHD than ADHD without comorbid DBDs²³. Siblings of individuals with ADHD + DBDs have a higher recurrence risk to develop ADHD + DBDs compared to siblings of individuals having ADHD without DBDs (ADHDwoDBDs)^{24,25}. Individuals with ADHD + DBDs also have an increased polygenic burden of common ADHD risk variants compared to individuals with only ADHD, further supporting the hypothesis that ADHD + DBDs reflect a higher load of genetic risk²⁶. However, it seems unlikely that ADHD risk variants alone can fully account for the underlying genetic risk that mediates aggressive and disruptive behaviors in individuals with ADHD + DBDs. Family studies have found that ADHD and DBDs have distinct genetic architectures with moderate to high genetic overlap in the range of 0.34–0.74^{27–29}. The existence of genetic risk factors specific to the aggressive and disruptive component of ADHD + DBDs finds support from a twin study, where DBDs had an estimated heritability of 0.33–0.64 after controlling for ADHD³⁰.

Several genome-wide association studies (GWASs) have focused on diagnosed DBDs^{31,32} or aggressive and anti-social behaviors^{33,34}, with only limited success in identifying genome-wide significant loci and no conclusive, replicated findings^{31,33,34}. Only two genome-wide studies have focused specifically on ADHD + DBDs. One small genome-wide linkage study examined DBDs in individuals with ADHD³⁵ and another, while not assessing diagnosed DBDs, examined aggressive behaviors in individuals with ADHD³⁶. Neither studies reported genome-wide significant loci.

In the current study we perform a large GWAS meta-analysis of ADHD + DBDs using a Danish nation-wide cohort from iPSYCH and samples from the Psychiatric Genomics Consortium (PGC). We identify three genome-wide significant loci for ADHD + DBDs, located on chromosomes 1, 7, and 11, and show evidence of transancestral association for the locus on chromosome 11 in a Chinese cohort and, we find high polygenic overlap

of ADHD + DBDs with childhood aggression and antisocial behavior in the general population, higher than found for ADHDwoDBDs.

Results

GWAS meta-analysis of ADHD + DBDs. The meta-analysis included data from the Danish iPSYCH cohort (2155 cases, 22,664 controls) and six European ancestry PGC cohorts (1647 cases, 8641 controls). All cases were diagnosed with both ADHD and DBDs or had a diagnosis of hyperkinetic conduct disorder, which according to the ICD10 criteria implies that both disorders are present. Selection of controls was population-based and they were not diagnosed with either ADHD or DBDs. Results were in total based on 3802 cases and 31,305 controls and included 8,285,688 variants after filtering. Three loci passed the threshold for genome-wide significance ($P = 5 \times 10^{-8}$); these were located on chromosome 1 (index variant rs549845, $P = 2.38 \times 10^{-8}$, OR = 1.16), 7 (index variant rs11982272, $P = 4.38 \times 10^{-8}$, OR = 0.83), and 11 (index variant, rs7118422, $P = 8.97 \times 10^{-9}$, OR = 1.16) (Table 1, Fig. 1a and Supplementary Fig. 1A–C). The directions of association of the index variants in the three loci were consistent across all cohorts (Supplementary Fig. 2A–C).

Homogeneity of effects in the PGC and iPSYCH cohorts and intercept evaluation. To evaluate the consistency of the genetic architecture underlying ADHD + DBDs in iPSYCH and PGC cohorts, we estimated the genetic correlation between the two using LD score regression^{37,38}. The genetic correlation between the iPSYCH cohort and the meta-analyzed PGC cohorts was high ($r_g = 0.934$, SE = 0.14, $P = 3.26 \times 10^{-11}$) supporting consistency of the ADHD + DBDs phenotypes analyzed in the cohorts. In addition, no variants demonstrated significant heterogeneity between studies (Supplementary Figs. 3 and 4).

LD score regression analysis indicated that the observed deviation of the genome-wide test statistics from the null distribution ($\lambda = 1.11$, Fig. 1b) was mainly caused by polygenicity. The intercept ratio estimate suggests that the majority of the inflation of the mean χ^2 statistic of the GWAS meta-analysis is attributable to polygenic effects (ratio = 0.12, SE = 0.0662) rather than confounding factors. The estimated remaining contribution of confounding factors was small and non-significant (intercept = 1.015; SE = 0.008; $P = 0.064$).

Transancestry GWAS meta-analysis across European and Han Chinese ancestry. To replicate and generalize the findings to other ethnicities, a GWAS of ADHD + DBDs was performed in a Han Chinese cohort (referred to as the Chinese cohort (406 cases, 917 controls; Supplementary Fig. 5). Of the three loci identified in the main analysis, the locus on chromosome 11 was nominally significant in the Chinese cohort ($P = 0.006$, Supplementary Fig. 8C). A fixed effects meta-analysis including the Chinese, European iPSYCH and PGC cohorts was performed in total including 4208 cases and 32,222 controls (no variants demonstrated significant heterogeneity across European and Chinese ancestries, Supplementary Figs. 6 and 7). For the locus on chromosome 11 the association P -value became stronger in the transancestry GWAS meta-analysis ($P = 3.15 \times 10^{-10}$, OR = 1.17) (Fig. 2 and Supplementary Data 1, Supplementary Fig. 9), suggesting the locus is a risk locus for ADHD + DBDs across ethnicities. The results incorporating the Chinese cohort did not support replication of the other two loci (Table 1).

Secondary GWASs. For subsequent evaluation of how much of the signal in the GWAS meta-analysis of ADHD + DBDs

Table 1 Results for the genome-wide significant index variants in the three loci associated with ADHD + DBDs.

SNP	Chr	Gene	A1	A2	iPSYCH+PGC			Chinese			iPSYCH+PGC + Chinese				
					FRQ	OR	SE	P	FRQ	OR	SE	P	FRQ	OR	SE
rs7118422	11	STIM1	T	C	0.51	1.164	0.026	8.97×10^{-9}	0.48	1.276	0.089	0.006	1.173	0.025	3.15×10^{-10}
rs549845	1	PTPRF	G	A	0.30	1.166	0.027	2.38×10^{-8}	0.31	0.943	0.095	0.541	1.147	0.026	2.179×10^{-7}
rs1198272	7	MAD1L1	T	C	0.78	1.199	0.033	4.39×10^{-8}	0.86	0.901	0.132	0.132	1.179	0.032	3.013×10^{-7}

Results from the GWAS meta-analysis of iPSYCH+PGC (European ancestry, 3802 cases and 31,305 controls), the transancestry GWAS meta-analysis (4208 cases and 32,222 controls) for identification of cross-ethnicity risk variants in Europeans and Chinese (iPSYCH + PGC + Chinese). The location (chromosome (chr)), gene location of index variant (Gene), alleles (A1 and A2), frequency of A1(FRO), odds ratio (OR) of the effect with respect to A1, and association P-values from inverse-variance weighted fixed effects model of the index variants are given.

was driven by the oppositional/aggressive component of the comorbid phenotype, two additional GWASs were conducted using iPSYCH samples. To adjust for the effect of ADHD, we performed a case-only GWAS comparing 1959 individuals with ADHD + DBDs against 13,539 individuals having ADHDwoDBDs, referred to as the “ADHD + DBDs vs. ADHDwoDBDs GWAS”. Additionally, a GWAS of 13,583 cases having ADHDwoDBDs and 22,314 population-based controls, referred to as the “ADHDwoDBDs GWAS”, was performed (the case-control numbers differ between GWASs due to deviation in the numbers of related individuals and genetic outliers removed in the analyses).

The summary statistics from the two secondary GWASs were used to evaluate the direction of association of the top loci (281 loci, $P < 1 \times 10^{-4}$) from the GWAS meta-analysis of ADHD + DBDs. A consistent direction of association was observed for 221 loci (out of the 281 loci) in the ADHDwoDBDs GWAS (sign test $P < 2.2 \times 10^{-16}$), while all the 281 loci demonstrated consistent direction of association in the ADHD + DBDs vs. ADHDwoDBDs GWAS. The proportion of variants having a consistent direction of association in the ADHD + DBDs vs. ADHDwoDBDs GWAS was significantly larger than the proportion in the ADHDwoDBDs GWAS ($P = 7.7 \times 10^{-16}$), which suggests that the associations in the GWAS meta-analysis of ADHD + DBDs reflects association with the comorbid phenotype beyond association with risk for ADHD alone.

All three genome-wide significant loci demonstrated higher effect sizes in ADHD + DBDs compared to ADHDwoDBDs (Supplementary Data 2). In particular, the effect sizes for the loci located on chromosomes 7 and 11 ($OR_{chr7} = ORs\ 1.199$; $OR_{chr11} = 1.164$) remained strong in the ADHD + DBDs vs. ADHDwoDBDs GWAS ($OR_{chr7} = 1.128$; $OR_{chr11} = 1.126$) confirming a stronger effect of the risk allele for these two loci in ADHD + DBDs compared to ADHDwoDBDs (Supplementary Data 2). The difference was most striking for rs7118422 on chromosome 11 (ADHD + DBDs: $OR = 1.164$, $P = 8.97 \times 10^{-9}$), which showed no evidence for association with ADHDwoDBDs ($OR = 1.022$, $P = 0.175$) versus a suggestive evidence of association with ADHD + DBDs vs. ADHDwoDBDs ($OR = 1.126$, $P = 7.07 \times 10^{-04}$).

To help formalize the comparison of ADHD + DBDs with ADHDwoDBDs, we also used mtCOJO³⁹ to estimate the joint effects of the significant loci from the GWAS of ADHD + DBDs conditional on effects mediated through the genetics of ADHDwoDBDs. Under this model (see “Methods” section) none of the three loci reached genome-wide significance for a direct effect on ADHD + DBDs, although the locus on chromosome 11 retained the most robust signal after correction for ADHDwoDBDs ($OR_{adjusted} = 1.14$; $P_{adjusted} = 1.43 \times 10^{-06}$, Supplementary Data 3).

Gene-based association test. A gene-based association analysis was performed using MAGMA⁴⁰. Six genes (*RRM1*, *STIM1*, *MAML3*, *ST3GAL3*, *KDM4A*, and *PTPRF*) were significantly associated with ADHD + DBDs ($P < 2.7 \times 10^{-6}$ correcting for 18,553 genes analyzed; Supplementary Fig. 10 and Supplementary Data 4). Three genes (*ST3GAL3*, *KDM4A*, and *PTPRF*) are located in the genome-wide significant locus on chromosome 1, and two genes (*RRM1*, *STIM1*) in the genome-wide significant locus on chromosome 11. One gene (*MAML3*) located on chromosome 4 had not been identified as a risk locus in the single variant analysis.

To evaluate if the gene-based association signals reflected the aggressive and disruptive component of the ADHD + DBDs phenotype rather than ADHD alone, we did a gene-set test of the

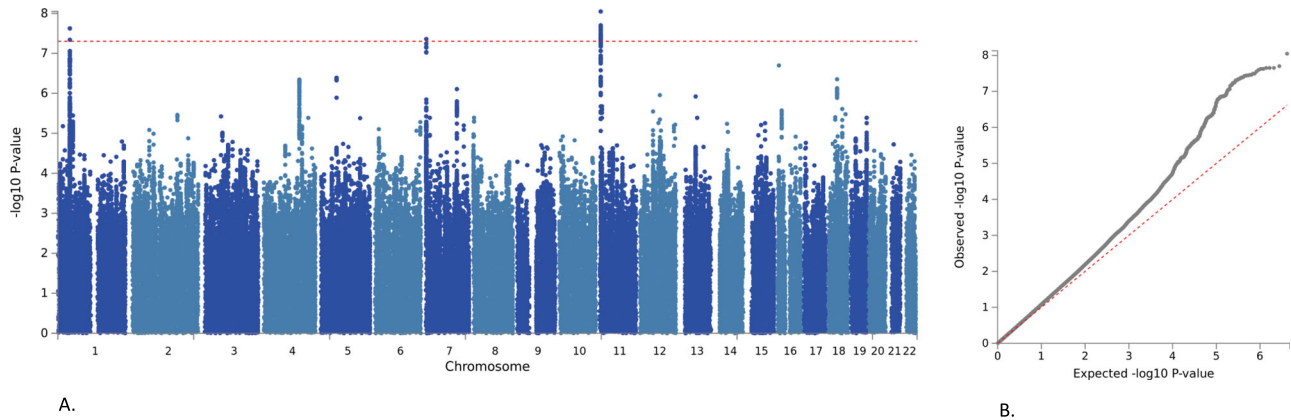


Fig. 1 Manhattan plot and quantile-quantile plot of results from the GWAS meta-analysis of ADHD + DBDs. **A** Results from GWAS meta-analysis of iPSYCH and PGC cohorts in total including 3802 cases and 31,305 controls. The x-axis represents autosomal chromosomes colored in light and dark blue. The y-axis represents two-sided P -values from meta-analysis using an inverse-variance weighted fixed effects model. The red horizontal line represents the threshold for genome-wide significant association ($P = 5 \times 10^{-8}$). **B** Quantile-quantile (q-q) plot with expected $-\log_{10} P$ -values on the x-axis and $-\log_{10} P$ -values from the GWAS meta-analysis on the y-axis. The dotted line indicates the distribution under the null hypothesis.

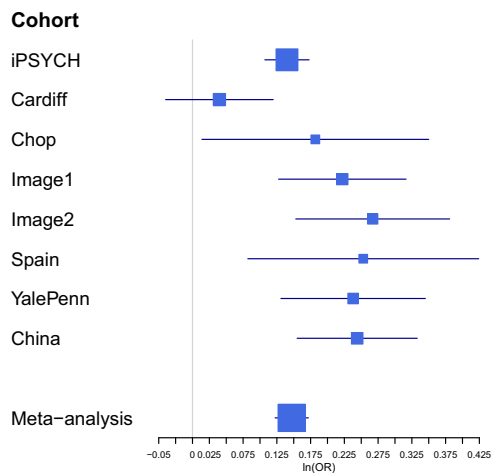


Fig. 2 Forest plot for the index variant (rs7118422) in the genome-wide significant locus on chromosome 11. Visualization of the effect size estimates (natural logarithm of the odds ratio (ln(OR))) in each included cohort, estimated from logistic regression, and in the trans-ancestry GWAS meta-analysis of European and Chinese cohorts (4208 cases and 32,222 controls) using an inverse-variance weighted fixed effects model. In addition, standard errors of the ln(OR) estimates. For information on sample sizes, allele frequencies and P -values for rs7118422 in the single cohorts see Supplementary Data 1.

most associated genes from the primary ADHD + DBDs GWAS meta-analysis ($P < 10^{-3}$, 79 genes) using the results from the two secondary GWASs. The gene set was significantly associated with ADHDwoDBDs (beta = 0.312 (SE = 0.02), $P = 9 \times 10^{-4}$), but had a stronger association in the ADHD + DBD vs. ADHD only GWAS (beta = 1.1 (SE = 0.07), $P = 9.28 \times 10^{-32}$).

Association of genetically regulated gene expression with ADHD + DBDs. Association of the genetically regulated gene expression with ADHD + DBDs was analyzed in 12 brain tissues from GTEx⁴¹ (version 6p) using MetaXcan⁴². Depending on the tissue, 2042–6094 genes were tested (Supplementary Data 5). Three genes were predicted to be differently expressed in ADHD + DBDs cases compared with controls after Bonferroni correction (correcting for the total number of tests performed (43,142); $P < 1.16 \times 10^{-6}$); *RRM1* (chromosome 11) was less expressed in

cases, while *RAB3C* (chromosome 5) and *LEPRE1* (chromosome 1) showed a higher expression in cases when compared to controls (Supplementary Data 5). The genes on chromosome 1 and 11 were located in or near genome-wide significant loci, whereas the gene on chromosome 5 was novel.

SNP heritability. SNP heritability (h^2_{SNP}) was estimated using a prevalence of ADHD + DBDs in the population of 1–2%, based on studies reporting that around 20–40% of individuals with ADHD have comorbid DBDs^{8–11}. The estimated h^2_{SNP} for ADHD + DBDs was 0.25 (SE = 0.03) using LD score regression³⁷ with a prevalence estimate of 2% in the population (Supplementary Data 6A). When considering only the iPSYCH cohort, a higher SNP heritability was found for ADHD + DBDs ($h^2_{\text{SNP}} = 0.34$; SE = 0.05) compared to ADHDwoDBDs ($h^2_{\text{SNP}} = 0.20$; SE = 0.02). This pattern remained similar when using GCTA and was stable when assuming a lower prevalence of ADHD + DBDs (1%) and higher prevalence of ADHDwoDBDs (3%) (Supplementary Data 6A). The h^2_{SNP} estimate was significantly higher for ADHD + DBDs compared to ADHDwoDBDs in GCTA analyses of independent iPSYCH samples, with $P_{\text{difference}} = 5.36 \times 10^{-6}$ when assuming a prevalence of 2% for ADHD + DBDs and 3% for ADHDwoDBDs (Supplementary Data 6B). Additionally, common variants explained a small fraction of the variation in the ADHD + DBDs phenotype compared to the ADHDwoDBDs phenotype (GCTA $h^2_{\text{SNP}} = 0.08$; SE = 0.04; Supplementary Data 6A).

Genetic correlation with aggression-related phenotypes. We estimated the genetic correlations of ADHD + DBDs with aggression-related phenotypes using GWAS results from analyses of aggressive behaviors in 18,988 children³³ (EAGLE aggression) and antisocial behavior in 16,400 individuals³⁴ (Broad Antisocial Behavior Consortium (BroadABC)) using LD score regression³⁷. We found a high genetic correlation of ADHD + DBDs with aggression in children (EAGLE aggression, $r_g = 0.81$; SE = 0.24; $P = 0.001$) and antisocial behavior (BroadABC, $r_g = 0.82$; SE = 0.30; $P = 0.007$) (Supplementary Data 7). In contrast, ADHDwoDBDs (analysed solely in iPSYCH) was only significantly correlated with aggression in children ($r_g = 0.74$; SE = 0.18; $P = 4.6 \times 10^{-5}$). Analyzing only the iPSYCH cohort, ADHD + DBDs demonstrated a nominally higher positive genetic correlation than ADHDwoDBDs with aggression in children ($r_g = 0.85$; SE = 0.24; $P = 5 \times 10^{-4}$; and $r_g = 0.74$;

SE = 0.18; $P = 4.58 \times 10^{-5}$, respectively) and antisocial behavior ($r_g = 0.92$; SE = 0.35; $P = 9 \times 10^{-3}$; and $r_g = 0.56$; SE = 0.22; $P = 0.01$, respectively). The differences in the genetic correlations, however, were not statistically significant when assessed using the jackknife method⁴³. Finally, we estimated the genetic correlation of ADHD + DBDs vs ADHDwoDBDs ($r_g = 0.99$, SE = 0.07, $P = 2.64 \times 10^{-45}$).

Polygenic score analysis of ADHD + DBDs compared to ADHDwoDBDs. Case-only polygenic score (PGS) analyses were done to evaluate whether ADHD + DBDs cases are enriched for variants associated with 22 relevant phenotypes related to personality, cognition, and psychiatric disorders compared with cases having ADHDwoDBDs. Seven phenotypes were significantly associated with ADHD + DBDs compared with ADHDwoDBDs after multiple testing correction (Supplementary Data 8). Significantly increased PGS for aggressive behavior³³ ($Z = 4.80$, $P = 1.51 \times 10^{-6}$, OR = 1.13) and ADHD ($Z = 5.42$, $P = 5.90 \times 10^{-8}$, OR = 1.21) were observed for ADHD + DBDs. Additionally, PGS for increased cognitive performance was negatively associated with ADHD + DBDs compared to ADHDwoDBDs (educational attainment⁴⁴, $Z = -3.30$, $P = 8.0 \times 10^{-4}$, OR = 0.92; college or university degree⁴⁵ $Z = -3.22$, $P = 1.0 \times 10^{-3}$, OR = 0.93; human intelligence⁴⁶ $Z = -3.00$, $P = 2.00 \times 10^{-3}$, OR = 0.93; verbal-numerical reasoning⁴⁵ $Z = -3.26$, $P = 1.00 \times 10^{-3}$, OR = 0.92). Finally, PGS for having children at an older age was negatively associated with ADHD + DBDs compared to ADHDwoDBDs ($Z = -4.40$, $P = 8.4 \times 10^{-6}$, OR = 0.9). Only a small proportion of the variance in ADHD + DBDs among individuals with ADHD was explained by the PGSs, with the maximum Nagelkerke's $R^2 = 0.36\%$ for the ADHD PGS. The odds ratio for ADHD + DBDs was increasing across quintiles of the polygenic load of variants associated with aggression, and ADHD, and decreasing with higher load of variants associated with cognition and age at first birth (Supplementary Fig. 11A–G). The highest risk was observed for ADHD PGS, where the 20% of ADHD cases with the highest ADHD PGS had an OR = 2.48 for having comorbid DBDs relative to the 20% with the lowest ADHD PGS (Supplementary Figure 11A).

Discussion

This study identifies genome-wide significant loci for ADHD + DBDs based on a meta-analysis of 3802 cases and 31,305 controls from the iPSYCH cohort and six cohorts from PGC. We identified three risk loci on chromosomes 1, 7, and 11 with odds ratios ranging from 1.16 to 1.20, in line with what was found in the recent GWAS meta-analysis of ADHD⁴⁷. These risk loci demonstrated high consistency in the direction of association in the included cohorts, indicating that the associations likely have a biological cause rather than being spurious signals driven by one or few cohorts (Fig. 2 and Supplementary Fig. 2A–C). The high genetic correlation observed between the PGC cohorts and the iPSYCH cohort suggests that the genetic architecture underlying ADHD + DBDs were similar in the two samples. In the GWAS meta-analysis for trans-ancestry risk of the identified loci in a Chinese sample, only the locus on chromosome 11 replicated the findings in the European samples. This locus seems to be specifically associated with the aggressive and disruptive component of the ADHD + DBDs phenotype, since the effect disappeared in the ADHDwoDBDs GWAS. This was further supported in the GWAS comparing comorbid ADHD + DBD to ADHDwoDBDs where the locus remained strongly associated, although not genome-wide significant (Supplementary Data 2). Consistent with this, evidence for a direct effect of the locus on ADHD +

DBDs remained after adjusting for the effect of ADHDwoDBDs in the mtCOJO analysis (Supplementary Data 3).

In contrast, the locus on chromosome 1, which was previously identified as a strong risk locus for ADHD⁴⁷, seems to reflect an association with ADHD. This locus remained genome-wide significant in the GWAS of ADHDwoDBDs (Supplementary Data 2) and the association with ADHD + DBDs decreased considerably in the analyses adjusting for the effect of ADHDwoDBDs and in the ADHD + DBDs vs. ADHDwoDBDs GWAS (Supplementary Data 2 and 3).

The locus on chromosome 7 seems to be a shared risk locus between ADHD + DBDs and ADHDwoDBDs. The locus remained moderately associated in the GWASs adjusted for ADHD (Supplementary Data 2 and 3) as well as in the ADHDwoDBDs GWAS (Supplementary Data 2). The locus is located in *MAD1L1*, which encodes a protein involved in mitotic spindle-assembly checking before anaphase. The locus is novel with respect to ADHD and DBDs, but was found genome-wide significant in the recent large cross-disorder GWAS⁴⁸ and has previously been associated with schizophrenia and bipolar disorder^{49–51}, suggesting that *MAD1L1* is a risk gene for several psychiatric disorders.

The locus most strongly associated with ADHD + DBDs on chromosome 11 is located in *STIM1* (Supplementary Fig. 1C), a gene not previously implicated in ADHD, DBDs, aggression-related phenotypes, or psychiatric disorders. *STIM1* encodes a transmembrane protein (STIM1) in the endoplasmic reticulum (ER) that acts as a sensor of calcium. Upon calcium depletion from the ER, STIM1 is responsible for an influx of calcium ions from the extracellular space through store-operated calcium channels to refill ER stores^{52–54}. Store-operated calcium entry may also be involved in neuronal calcium signaling⁵⁵, and recent evidence indicates that STIM1 plays a role in synaptic plasticity affecting learning and memory^{55,56}. These results are interesting in the light of the observed learning deficits associated with aggressive behaviors and accumulating evidence that suggests calcium signaling is involved in several psychiatric disorders^{57–59}. Alternatively, analysis of genetically regulated gene expression suggested that the variants in the genome-wide significant locus might affect expression of *RRM1*, with a decreased *RRM1* expression being associated with ADHD + DBDs. *RRM1* is oriented in a tail-to-head configuration with *STIM1*, which lies 1.6 kb apart, and encodes a subunit of a reductase involved in the biosynthesis of deoxyribonucleotides from the corresponding ribonucleotides necessary for DNA replication. To our knowledge, this gene has not previously been associated with psychiatric disorders.

In the gene-based analysis six genes were exome-wide significantly associated with ADHD + DBDs, including two implicated by variants in or near the genome-wide significant locus on chromosome 11 (*RRM1* and *STIM1*) and with three (*ST3GAL3*, *KDM4A*, and *PTPRF*) out of the remaining four located in or near the genome-wide significant locus on chromosome 1. The top-associated genes (79 genes) seem to mainly reflect association with the aggressive and disruptive component of the ADHD + DBDs phenotype. The geneset was significantly associated with ADHDwoDBDs but even more strongly associated in the ADHD + DBDs vs. ADHDwoDBDs GWAS (where the effect of ADHD is corrected out). Likewise, the most strongly associated single markers (with $P < 1 \times 10^{-4}$) in the GWAS meta-analysis of ADHD + DBDs showed high consistency in the direction of association in the GWAS of ADHDwoDBDs, but even higher consistency in the ADHD + DBDs vs. ADHDwoDBDs GWAS, reinforcing the notion that the associations mainly reflect the aggressive and disruptive component of the phenotype.

When evaluating the polygenic architecture of ADHD + DBDs, a higher SNP heritability was found for ADHD + DBDs

($h^2_{\text{SNP}} = 0.34$; SE = 0.05) compared to ADHDwoDBDs ($h^2_{\text{SNP}} = 0.2$; SE = 0.02) (Supplementary Data 6A and 6B). These estimates are consistent with the recently reported SNP heritability of ADHD ($h^2_{\text{SNP}} = 0.22$; SE = 0.01)⁴⁷, which included individuals with and without comorbid DBDs. Conditional on an ADHD diagnosis, the aggressive and disruptive behavioral component of the ADHD + DBDs phenotype also has a genetic component involving common variants ($h^2_{\text{SNP}} = 0.08$; SE = 0.04). PGS analyses suggested the higher SNP heritability of ADHD + DBDs compared to ADHDwoDBDs is partly explained by a higher burden of common ADHD risk variants (Supplementary Data 8). The significantly higher burden of ADHD risk variants among individuals with ADHD + DBDs was especially evident when examining individuals belonging to the 20% of ADHD cases with the highest ADHD genetic risk load, who had an odds ratio of 2.48 for having comorbid DBDs (Supplementary Fig. 11A). This is also a replication of previous findings of a higher load of ADHD risk variants in individuals with ADHD and comorbid conduct disorder compared to those having only ADHD²⁶.

Going beyond ADHD risk burden, the common variant component of ADHD + DBDs could also include variants mainly associated with aggression. This idea is supported by our finding of increased PGS for aggression in ADHD + DBDs compared to ADHDwoDBDs (Supplementary Fig. 11B). This conclusion is reinforced by the genetic correlation results, where we found somewhat higher genetic correlation of ADHD + DBDs with both aggressive behavior in children³³ and antisocial behavior³⁴ (Supplementary Data 7) compared to those found for ADHDwoDBDs. Additionally, these results imply that the genetic architecture underlying the aggressive and disruptive behavioral component of the ADHD + DBDs phenotype overlaps strongly with that affecting aggressive and antisocial behavior in the general population. Thus, aggressive and antisocial behaviors seem to have a continuous distribution in the population, with individuals having ADHD + DBDs representing an extreme. This is in line with what has been observed for other complex phenotypes, such as diagnosed ADHD representing the upper tail of impulsive and inattention behaviors⁴⁷, and diagnosed autism spectrum disorder representing the upper tail for social communication difficulties and rigidity^{60,61}.

Aggressive behavior is stable across age intervals during childhood⁶², and twin studies have suggested genetics play an important role in this stability^{62,63}. Moreover, early aggression might be predictive of later serious antisocial behavior⁶⁴ resulting in increased risk of a diagnosis of antisocial personality disorder⁶⁵. Our results suggest that common genetic variants play an important role in childhood aggression, which has also been reported previously³³, and that the subsequent risk for antisocial behavior in individuals with ADHD + DBDs to some extent has an underlying genetic cause involving common variants. However, our results do not reveal whether the increased polygenic load of variants associated with aggression observed in ADHD + DBDs is caused by variants specific to DBDs or due to a general increased load of variants that are also shared with ADHD.

It should also be noted that the SNP heritabilities of childhood aggression³³ and antisocial behavior³⁴ are at the low end (0.05 and 0.06, respectively), and probably biased downwards by heterogeneity in the cohorts analyzed³³. The studies do therefore not capture the full impact of common variants in aggressive behavior, and the observed high genetic correlation of the two phenotypes with ADHD + DBDs involves variants that only explain a small proportion of variance in aggression.

We have shown that individuals with ADHD + DBDs have an increased load of variants associated with worse cognition compared to individuals having ADHDwoDBDs (Supplementary Data 8 and Supplementary Fig. 11C–F). This could reflect the

increased genetic load of ADHD risk variants in ADHD + DBDs, since ADHD has a strong negative genetic correlation with cognition-related phenotypes⁴⁷. However, it might also involve variants associated with antisocial behavior, which also has a negative genetic correlation with educational performance³⁴. This latter idea is consistent with epidemiological studies linking aggression to decreased educational attainment^{66–68}. Finally, we found a significantly higher load of variants associated with younger age at birth of first child in ADHD + DBDs compared to ADHDwoDBDs, in line with the observed positive genetic correlations of ADHD and antisocial behavior with having children earlier^{34,47} and evolutionary theories suggesting that aggression has played a role when competing for access to mates⁶⁹.

In summary, we identified three genome-wide significant loci for ADHD + DBDs. The locus on chromosome 11 was associated most strongly with the comorbid phenotype, and seems to be a cross-ancestry risk locus in Europeans and Chinese. Our results suggest that the aggressive and disruptive behavioral component of the ADHD + DBDs phenotype has a genetic risk component, which in part include common risk variants associated with ADHD, aggressive, and antisocial behavior. Individuals with ADHD + DBDs therefore represent a phenotype with an increased genetic risk load compared to ADHDwoDBDs, including at least one genome-wide significant locus specific to ADHD + DBDs. This study represents the first step towards a better understanding of the biological mechanism underlying ADHD + DBDs.

Methods

Samples—the iPSYCH cohort. The iPSYCH cohort is a population-based nationwide cohort which includes 79,492 genotyped individuals (~50,000 diagnosed with major psychiatric disorders and ~30,000 controls). The cohort was selected, based on register information from a baseline birth cohort of all singletons born in Denmark between May 1st, 1981 and December 31, 2005 ($N = 1,472,762$) (see a detailed description in the ref.⁷⁰). A biological sample of the included individuals were obtained from the Newborn Screening Biobank at Statens Serum Institute, Denmark. DNA was extracted from dried blood spot samples and whole genome amplified in triplicates^{71,72}. Genotyping and calling of genotypes were performed as described in our previous publications^{47,70}.

For this study cases and controls were identified based on diagnoses given in 2016 or earlier in the Danish Psychiatric Central Research Register⁷³. Cases with ADHD + DBDs had a diagnosis of hyperkinetic conduct disorder (F90.1) or an ADHD diagnosis (ICD-10 F90.0) occurring together with a diagnosis of ODD (ICD-10 F91.3) or conduct disorder (ICD-10 F91.0, F91.1, F91.2, F91.8, and F91.9). Distribution of cases with ADHD + DBDs over diagnosis codes is presented in Supplementary Data 9. ADHD cases without DBDs were defined as individuals having ADHD (ICD-10 F90.0) without any diagnosis of DBDs. Controls were randomly selected from the same nation-wide birth cohort and not diagnosed with ADHD or DBDs.

The study was approved by the Danish Data Protection Agency and the Scientific Ethics Committee in Denmark. All analyses of the iPSYCH cohort were performed at the secured national high performance-computing cluster, GenomeDK (<https://genome.au.dk>).

Samples—cohorts from the Psychiatric Genomics Consortium. For the meta-analysis, seven ADHD cohorts (six cohorts of European ancestry and one of Chinese ancestry) provided by PGC with information about diagnoses of ADHD + DBDs were included. An overview of the cohorts including genotyping information and diagnosis criteria can be found in Supplementary Data 10. Detailed descriptions of the cohorts can be found elsewhere⁷⁴. Details on approval authorities can be found in Supplementary Data 10.

Quality control and imputation. Quality control, imputation, and primary GWASs of the iPSYCH and PGC cohorts (including the Chinese cohort) were done separately for each using the bioinformatics pipeline Ricopili⁷⁵. Pre-imputation quality control allowed an inclusion of individuals with a call rate > 0.98 (> 0.95 for iPSYCH) and genotypes with a call rate > 0.98, difference in SNP missingness between cases and controls < 0.02, no strong deviation from Hardy–Weinberg equilibrium ($P > 1 \times 10^{-6}$ in controls or $P > 1 \times 10^{-10}$ in cases) and low individual heterozygosity rates ($|F_{\text{het}}| < 0.2$). Genotypes were phased and imputed using SHAPEIT⁷⁶ and IMPUTE2⁷⁷ and the 1000 Genomes Project phase 3 (1KGP3)⁷⁸ as imputation reference panel (the East Asian reference genome was used for

imputation of the Chinese samples). Trio imputation was done with a case-pseudocontrol setup.

Relatedness and population stratification were evaluated using a set of high-quality genotyped markers (minor allele frequency (MAF) > 0.05, HWE $P > 1 \times 10^{-4}$ and SNP call rate > 0.98) pruned for linkage disequilibrium (LD) resulting in ~30,000 pruned variants (variants located in long-range LD regions defined by Price et al.⁷⁹ were excluded). Genetic relatedness was estimated using PLINK v1.9^{80,81} to identify first and second-degree relatives ($\hat{\pi} > 0.2$) and one individual was excluded from each related pair (cases preferentially retained over controls). Genetic outliers were excluded based on principal component analyses (PCA) using EIGENSOFT^{82,83}. For iPSYCH a genetic homogenous sample was defined based on a subsample of individuals being Danes for three generations as described in Demontis and Walters et al.⁴⁷. For the PGC samples genetic outliers were removed based on visual inspection of the first six PCs. For all cohorts PCA was redone after exclusion of genetic outliers.

GWAS meta-analysis and transancestry risk in European and Chinese ethnicities. Association analysis was done in PLINK⁸⁰ using additive logistic regression and the imputed marker dosages, covariates from principal component analyses (after removal of genetic outliers) and other relevant covariates (Supplementary Data 10). Meta-analysis of the iPSYCH cohort (2155 cases, 22,664 controls) and the six PGC cohorts (1647 cases, 8641 controls) was done using an inverse standard error weighted fixed effects model and the software METAL⁸⁴ and included in total 3802 cases and 31,305 controls.

For transancestry genetic risk variants in European and Chinese cohorts, a GWAS meta-analysis was done as described above including the iPSYCH cohort, the six European PGC cohorts and the cohort of Chinese ancestry. In total, 4208 cases and 32,222 controls were included. No individual genotypes were used for the meta-analysis.

In the two meta-analyses only variants with MAF > 0.01 and imputation INFO score > 0.8 were included. All variants that were not supported by an effective sample size of 70% in the meta-analysis output were filtered out.

Homogeneity of effects in the PGC and iPSYCH cohorts and intercept evaluation. LD score regression^{37,38} was used to estimate the genetic correlation using summary statistics from GWAS of ADHD + DBDs in the iPSYCH cohort and meta-analysis of the six European PGC cohorts. Only variants with an imputation info score > 0.9 were included. The intercept was restricted to one as there was no sample overlap and no indication of population stratification.

The ratio (ratio = (intercept - 1)/(mean $\chi^2 - 1$)) from LD score regression was used to evaluate the relative contribution of polygenic effects and confounding factors to the observed deviation from the null in the genome-wide distribution of the χ^2 statistics of the GWAS meta-analysis of ADHD + DBDs.

Secondary GWASs. In order to adjust for the effect of ADHD we did a case-only GWAS comparing 1,959 individuals having ADHD + DBDs against 13,539 individuals having ADHDwoDBDs, referred to as the “ADHD + DBDs vs. ADHDwoDBDs GWAS”. Additionally, a GWAS of 13,583 cases having ADHDwoDBDs and 22,314 population-based controls referred to as the “ADHDwoDBDs GWAS” was performed. Both GWASs were based only on iPSYCH samples and performed using additive logistic regression and the imputed marker dosages, covariates from principal component analyses (after removal of genetic outliers) and covariates indicating genotyping waves.

The summary statistics from the two secondary GWASs were used to evaluate direction of association of the top loci associated with ADHD + DBDs using a sign test based on LD distinct variants ($r^2 < 0.2$, 281 variants) with association P -values less than 1×10^{-4} in the GWAS meta-analysis of ADHD + DBDs.

We also did an mtCOJO³⁹ analysis to estimate the effect of the top loci for ADHD + DBDs conditional on genetic effects on ADHD alone. This was done using summary statistics from the GWAS meta-analysis of ADHD + DBDs and from the GWAS of ADHDwoDBDs. The analysis was run using mtCOJO³⁹ implemented in GCTA⁸⁵ using standard procedures. Following default settings, estimation of the effect of ADHDwoDBDs on ADHD + DBDs (as part of the indirect path contributing to marginal ADHD + DBDs associations) was performed using variants that were genome-wide significant in the GWAS of ADHDwoDBDs ($P < 5 \times 10^{-8}$), and not in linkage disequilibrium ($r^2 < 0.05$; 7 index variants). No variants were removed due to evidence of pleiotropy (HEIDI-outlier threshold of $P = 0.01$).

Gene-based association test. Gene-based association analysis was done using MAGMA 1.05⁴⁰ and summary statistics from the GWAS meta-analysis. Variants were annotated to genes using the NCBI37.3 gene definitions and no window around genes was used. MAGMA summarizes association signals observed for variants located in a gene into a single P -value while correcting for LD in a reference genome. For this the European samples from the 1000 Genomes phase 3 were used.

The most associated genes in the GWAS meta-analysis of ADHD + DBDs (79 genes, $P < 10^{-3}$ Supplementary Data 4) were evaluated in a gene-set test for association with ADHD + DBDs compared to ADHDwoDBDs and for association

with ADHDwoDBDs. Gene-based P -values were generated using summary statistics from the two secondary GWASs (ADHD + DBDs vs. ADHD-only GWAS and ADHDwoDBDs GWAS) and subsequently gene-set tests were done using MAGMA 1.05⁴⁰. MAGMA performs a competitive test to analyze if the gene set is more strongly associated with the phenotype than other genes, while correcting for a series of confounding effects such as gene length and size of the gene set.

Association of the genetically regulated gene expression with ADHD + DBDs.

Association of the genetically regulated gene expression with ADHD + DBDs was analyzed in 12 brain tissues from GTEx⁸⁶ (version 6p) using MetaXcan⁴² implemented in the R-package metaxcanr (<https://github.com/drveera/metaxcanr>). MetaXcan is an extension of PrediXcan⁸⁷ that can be used to test for differences in gene expression using summary statistics. We used high-performance prediction models for MetaXcan based on variants located within 1 Mb +/- of transcription start site and trained using elastic net regression and 10-fold cross-validation⁴ downloaded from <http://predictdb.org>. MetaXcan also requires covariance matrices of the variants within each gene model for each tissue. Covariance matrices calculated from 503 individuals with European ancestry from the 1000 genomes project⁸⁸ available with the prediction models at <http://predictdb.org> were used.

SNP heritability. The SNP heritability (h^2_{SNP}) was estimated using LD score regression³⁷ and the summary statistics from the GWAS meta-analysis of ADHD + DBDs. The heritability was estimated on the liability scale assuming a population prevalence of ADHD + DBDs of 2 and 1%.

In order to evaluate the extent to which common genetic variants contributes to the risk of ADHD + DBDs compared to having ADHDwoDBDs, the SNP heritability of for the two phenotypes were estimated only in iPSYCH samples. This was done using LD score regression and univariate GREML analyses in GCTA⁸⁵. h^2_{SNP} was estimated on the liability scale assuming a population prevalence of 2 and 1% for ADHD + DBDs and 3 and 4% for ADHDwoDBDs. The GCTA analyses were corrected for the same covariates as used in the GWASs.

In order to be able to test for difference in h^2_{SNP} between ADHD + DBDs and ADHDwoDBDs we re-estimated h^2_{SNP} using GCTA based on independent iPSYCH controls. For this analysis the iPSYCH controls were split randomly into two groups within each genotyping wave. One group was used as controls for estimating h^2_{SNP} of ADHD + DBDs (2155 cases and 11,659 controls) and the other group was used to estimate h^2_{SNP} of ADHDwoDBDs (13,583 cases and 11,250 controls). The analysis using independent controls was done using prevalences of 2 and 1% for ADHD + DBDs and 3 and 4% for ADHDwoDBDs. Test for difference in h^2_{SNP} between ADHD + DBDs and ADHDwoDBDs was done using Eq. 1 below:

$$Z_{\text{diff}} = \left(h^2_{\text{SNP}(\text{ADHD}+\text{DBDs})} - h^2_{\text{SNP}(\text{ADHDwoDBDs})} \right) / \sqrt{\text{SE}_{(\text{ADHD}+\text{DBDs})}^2 + \text{SE}_{(\text{ADHDwoDBDs})}^2}, \quad (1)$$

where Z_{diff} is the Z-score for the difference in h^2_{SNP} and SE is the standard errors for the heritabilities. We calculated two-tailed P -values in R.

Additionally, we evaluated how much of the variance in the ADHD + DBDs phenotype could be explained by common genetic variation in the context of ADHD. For this we did a case-only approach including 1959 cases with ADHD + DBDs and 13,539 individuals with ADHDwoDBDs. This was only done using GCTA due to a low polygenic signal in the ADHD + DBDs vs. ADHDwoDBDs GWAS (mean $\chi^2 = 1.06$).

Genetic correlation with aggression-related phenotypes. The genetic overlap of ADHD + DBDs with aggression-related phenotypes was evaluated by estimating genetic correlations using LD score regression³⁷ and the summary statistics from the GWAS meta-analysis of ADHD + DBDs and results from two aggression related GWASs. One is a GWAS meta-analysis of scores of aggressive behaviors in 18,988 children³³ (EAGLE aggression) obtained by questionnaires filled by their parents. Another is a GWAS meta-analysis of antisocial behavior conducted by the Broad Antisocial Behavior Consortium (BroadABC) including 16,400 individuals³⁴. Both children and adults were accessed for a broad range of antisocial measures, including aggressive and non-aggressive domains. The BroadABC study has a minor overlap with the EAGLE aggression GWAS with respect to the included cohorts. We also estimated the genetic correlations of ADHDwoDBDs and ADHD+DBDs (only including iPSYCH individuals) with the two aggression-related phenotypes.

The genetic correlation between ADHD + DBDs and ADHDwoDBDs was calculated using LD score regression and summary statistics from the GWAS meta-analysis of ADHD + DBDs and the GWAS of ADHDwoDBDs, the latter based on iPSYCH data only. To supplement the LD score regression analysis we used iPSYCH genotypes and GCTA to estimate the genetic correlation between ADHD + DBDs (2155 cases and 11,659 controls) and ADHDwoDBDs (13,583 cases and 11,250 controls), showing results consistent with LD score regression ($r_g = 0.97$; SE = 0.06), and not statistically different from one.

Statistical difference between two r_g estimates was calculated using the block jackknife method⁴³ implemented in the LD score regression software^{37,89}. The variants across the genome were divided in 200 blocks and jackknife deleted values were calculated by excluding one block at a time. The computed jackknife deleted

values were then used to calculate corresponding jackknife pseudo values. By using the mean and variance of the jackknife pseudovalues, Z-score and corresponding P-values were computed, testing the null hypothesis that the difference between the r_g s is equal to zero.

Polygenic score analysis. Case-only polygenic score (PGS) analyses were done using GWAS summary statistics from 22 GWASs related to cognition and education (six phenotypes), personality (nine phenotypes), psychiatric disorders (five phenotypes), reproduction/fitness (two phenotypes) (detailed list of phenotypes see Supplementary Data 3). Variants with imputation info score < 0.9 , MAF < 0.01 , missing values, ambiguous and multiallelic variants, indels and duplicated identifiers were removed. The remaining variants were LD-clumped using Plink⁸⁰. PGS was estimated at different P-value thresholds in the 22 training datasets: $P < 5 \times 10^{-8}$, 1×10^{-6} , 1×10^{-4} , 1×10^{-3} , 0.01, 0.05, 0.1, 0.2, 0.5, and 1.0. PGS in the target individuals (iPSYCH samples: 1959 ADHD + DBDs cases and 13,539 ADHDwoDBDs cases) were estimated multiplying the natural log of the odds ratio of each variant by the allele-dosage of each variant and whole-genome PGS was obtained by summing values over variants for each individual. The ADHD PGS was generated using the approach described in Demontis et al.⁴⁷; in short ADHD cases and controls in the iPSYCH cohort were split into five independent samples, then one sample was left out in an ADHD GWAS meta-analysis of iPSYCH data and data from the Psychiatric Genetics Consortium. The results were then used as training for generating PGS in the sample that was left out. This “leave-one sample out” procedure was repeated until ADHD PGSs were generated for all individuals in the iPSYCH cohort. For each P-value threshold the variance in the ADHD + DBDs phenotype explained by PGS was estimated using Nagelkerke’s R^2 (R package “BaylorEdPsych”) and conversion to Nagelkerke’s R^2 on the liability scale was done using the method suggested by Lee et al.⁹⁰ and a prevalence of 0.2 for comorbid DBDs among ADHD cases. Association of PGS with ADHD + DBDs compared to ADHDwoDBDs was estimated using logistic regression including the same covariates used in the GWAS.

Subsequently individuals were divided into quintiles based on their PGS. OR for ADHD + DBDs compared to ADHDwoDBDs was estimated within each quintile with reference to the lowest risk quintile (using the training data P-value threshold resulting in the highest Nagelkerke’s R^2 in the target data).

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All relevant iPSYCH data are available from the authors after approval by the iPSYCH Data Access Committee and can only be accessed on the secured Danish server as the data are protected by Danish legislation. Access to data provided by the Psychiatric Genomics Consortium can be granted through the Psychiatric Genomics Data Access Committee <https://www.med.unc.edu/pgc/about-us/people/data-access-committee/>. For data access please contact: Ditte Demontis, email: ditte@biomed.au.dk, Anders D. Borglum, email: anders@biomed.au.dk. The summary statistics with the results from the GWAS meta-analysis of ADHD + DBDs are available on the iPSYCH website (<https://ipsych.dk/en/research/downloads/>).

Code availability

MetaXcan analysis was performed using the R-package metaxcan (<https://github.com/drveera/metaxcan/>), and GTEX v6p expression prediction models and covariance matrices downloaded from <http://predictdb.org>.

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D.D., S.V.F., and A.D.B. conceived the idea, supervised and directed the study. I.D.W., M. R., J.B.-G., M.B.-H., T.W., O.M., P.B.M., M.N., PGC-ADHD Consortium, B.C., D.M.H., B.M.N., B.F., S.V.F. and A.D.B. provided samples and/or data. D.D., R.K.W., V.M.R., I.D. W., J.G., and T.D.A. performed the analyses. D.D. wrote the manuscript. D.D., R.K.W., B. C., S.V.F., and A.D.B. comprised the core revision group. All authors discussed the results and approved the final version of the manuscript.

Competing interests

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Additional information

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