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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 = 3.15×10⁻¹⁰, OR = 1.17). We find a higher SNP heritability for ADHD + DBDs (h²SNP = 0.34) when compared to ADHD without DBDs (h²SNP = 0.20), high genetic correlations between ADHD + DBDs and aggressive (rG = 0.81) and anti-social behaviors (rG = 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.

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Atention-Deficit/Hyperactivity Disorder (ADHD) is a common childhood onset behavioral disorder affecting around 5% of children and 2.5% of adults. Comorbidity with other psychiatric disorders is common among children with ADHD, and disruptive behavior disorders (DBDs) are the most frequently co-occurring conditions. 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 violations. DBDs have a prevalence of 3–10%, among children and, are around twice as frequent in males compared to females and DBDs are associated with a 3-fold increased risk of premature death, with higher mortality rates than in ADHD. 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) while a study of 1.92 million individuals from Denmark found that 17% of those with ADHD were also diagnosed with DBDs. Among those with DBDs in the same Danish cohort, more than half (57%) had a comorbid diagnosis of ADHD. 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, in-patient psychiatric admission, transgression, risky behavior, and premature death compared to those diagnosed with ADHD only.

Both genetic and environmental factors influence the risk for ADHD and DBDs with twin heritability estimates of 0.71 and 0.40–0.70, respectively. Twin studies have also suggested that ADHD + DBDs is a more severe and genetically loaded subtype of ADHD than ADHD without comorbid DBDs. 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). 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 risk. 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. 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 ADHD.

Several genome-wide association studies (GWASs) have focused on diagnosed DBDs or aggressive and anti-social behaviors, with only limited success in identifying genome-wide significant loci and no conclusive, replicated findings. Two genome-wide studies have focused specifically on ADHD + DBDs. One small genome-wide linkage study examined DBDs in individuals with ADHD and another, while not assessing diagnosed DBDs, examined aggressive behaviors in individuals with ADHD. 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 (\(P = 5 	imes 10^{-8}\)), 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. The genetic correlation between the iPSYCH cohort and the meta-analyzed PGC cohorts was high (\(r_g = 0.934\), SE = 0.014, \(P = 3.26 \times 10^{-11}\)) 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 estimate suggests that the majority of the inflation of the mean \(\chi^2\) 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 (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
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, $P = 8.97 \times 10^{-5}$), 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 y-axis represents autosomal chromosomes colored in light and dark blue. The x-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 × 10⁻⁸). B. Quantile-quantile (q-q) plot with expected −log10 P-values on the x-axis and −log10 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 in the genome-wide significant locus for ADHD + DBDs on chromosome 11. 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 (In(OR))) in each included cohort, estimated from logistic regression, and in the trans-ancestry GWAS meta-analysis of European and Chinese cohorts (2028 cases and 32,222 controls) using an inverse-variance weighted fixed effects model. In addition, standard errors of the In(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 < 10⁻⁶, 79 genes) using the results from the two secondary GWASs. The gene set was significantly associated with ADHDDwoDBDs (beta = 0.312 (SE = 0.02), P = 9 × 10⁻⁴), but had a stronger association in the ADHD + DBD vs. ADHD only GWAS (beta = 1.1 (SE = 0.07), P = 9.28 × 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 MetaXcan. 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 × 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 (h²SNP) 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 DBDs4–6. The estimated h²SNP for ADHD + DBDs was 0.25 (SE = 0.03) using LD score regression7 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 (h²SNP = 0.34; SE = 0.05) compared to ADHDDwoDBDs (h²SNP = 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 ADHDDwoDBDs (3%) (Supplementary Data 6A). The h²SNP estimate was significantly higher for ADHD + DBDs compared to ADHDDwoDBDs in GCTA analyses of independent iPSYCH samples, with Pdiff-est = 5.36 × 10⁻⁶ when assuming a prevalence of 2% for ADHD + DBDs and 3% for ADHDDwoDBDs (Supplementary Data 6B). Additionally, common variants explained a small fraction of the variation in the ADHD + DBDs phenotype compared to the ADHDDwoDBDs phenotype (GCTA h²SNP = 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 regression35. We found a high genetic correlation of ADHD + DBDs with aggression in children (EAGLE aggression, r_g = 0.81; SE = 0.04; P = 0.001) and antisocial behavior (BroadABC, r_g = 0.87; SE = 0.07; Supplementary Data 7). In contrast, ADHDDwoDBDs (analysed solely in iPSYCH) was only significantly correlated with aggression in children (r_g = 0.74; SE = 0.18; P = 4.6 × 10⁻⁵). Analyzing only the iPSYCH cohort, ADHD + DBDs demonstrated a nominally higher positive genetic correlation than ADHDDwoDBDs with aggression in children (r_g = 0.85; SE = 0.24; P = 5 × 10⁻⁴; and r_g = 0.74;
Polygenic score analysis of ADHD + DBDs compared to ADHDwDBDs. 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 ADHDwDBDs. Seven phenotypes were significantly associated with ADHD + DBDs compared with ADHDwDBDs after multiple testing correction (Supplementary Data 8). Significantly increased PGS for aggressive behavior (Z = 4.80, P = 1.51 × 10^-6, OR = 1.13) and ADHD (Z = 5.42, P = 5.90 × 10^-8, OR = 1.21) were observed for ADHD + DBDs. Additionally, PGS for increased cognitive performance was negatively associated with ADHD + DBDs compared to ADHDwDBDs (educational attainment Z = -3.30, P = 8.0 × 10^-4, OR = 0.92; college or university degree Z = -3.22, P = 1.0 × 10^-3, OR = 0.93; human intelligence Z = -3.00, P = 2.00 × 10^-3, OR = 0.93; verbal-numerical reasoning Z = -3.26, P = 1.00 × 10^-3, OR = 0.92). Finally, PGS for having children at an older age was negatively associated with ADHD + DBDs compared to ADHDwDBDs (Z = -4.40, P = 8.4 × 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 R² = 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 ADHID, 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 2.10, in line with what was found in the recent GWAS meta-analysis of ADHD.87 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 ADHDwDBDs GWAS. This was further supported in the GWAS comparing comorbid ADHD + DBD to ADHDwDBDs 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 ADHDwDBDs in the mtCOJO analysis (Supplementary Data 3).

In contrast, the locus on chromosome 1, which was previously identified as a strong risk locus for ADHD,77 seems to reflect an association with ADHD. This locus remained genome-wide significant in the GWAS of ADHDwDBDs (Supplementary Data 2) and the association with ADHD + DBDs decreased considerably in the analyses adjusting for the effect of ADHDwDBDs and in the ADHD + DBDs vs. ADHDwDBDs GWAS (Supplementary Data 2 and 3).

The locus on chromosome 7 seems to be a shared risk locus between ADHD + DBDs and ADHDwDBDs. The locus remained moderately associated in the GWASs adjusted for ADHD (Supplementary Data 2 and 3) as well as in the ADHDwDBDs GWAS (Supplementary Data 2). The locus is located in MADI11, 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 GWAS49 and has previously been associated with schizophrenia and bipolar disorder49–51, suggesting that MADI11 is a risk gene for several psychiatric disorders.

The locus most strongly associated with ADHD + DBDs on chromosome 11 is located in STIMI (Supplementary Fig. 1C), a gene not previously implicated in ADHD, DBDs, aggression-related phenotypes, or psychiatric disorders. STIMI 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 stores52–54. 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 memory55,56. 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 disorders57–59. Alternatively, analysis of genetically regulated gene expression suggested that the variants in the genome-wide significant locus might affect expression of RRMI, with a decreased RRMI expression being associated with ADHD + DBDs. RRMI 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 (RRMI and STIM1) and with three (ST3GAL3, KDM4A, and PTPRF) out of the remaining four located in or near the genome-wide significant loci 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 gene set was significantly associated with ADHDwDBDs but even more strongly associated in the ADHD + DBDs vs. ADHDwDBDs GWAS (where the effect of ADHD is corrected out). Likewise, the most strongly associated single markers (with P < 1 × 10^-6) in the GWAS meta-analysis of ADHD + DBDs showed high consistency in the direction of association in the GWAS of ADHDwDBDs, but even higher consistency in the ADHD + DBDs vs. ADHDwDBDs 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 (\(h^2_{\text{SNP}} = 0.22; SE = 0.01\))\(^{67}\), 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 (\(h^2_{\text{SNP}} = 0.08; SE = 0.04\)). PCA 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 ADHD\(^{26}\).

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 children\(^{33}\) and antisocial behavior\(^{34}\) (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 behaviors\(^{37}\), 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 childhood\(^{62}\), 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 behavior\(^{44}\) resulting in increased risk of a diagnosis of antisocial personality disorder\(^{65}\). Our results suggest that common genetic variants play an important role in childhood aggression, which has also been reported previously\(^{33}\), 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 aggression\(^{33}\) and antisocial behavior\(^{44}\) are at the low end (0.05 and 0.06, respectively), and probably biased downwards by heterogeneity in the cohorts analyzed\(^{33}\). 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–E). 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 phenotypes\(^{47}\). However, it might also involve variants associated with antisocial behavior, which also has a negative genetic correlation with educational performance\(^{64}\). 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 the NHIS 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 mates\(^{69}\).

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 mechanisms 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 psychotropic 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. \(^{72}\)). 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\(^{72,77}\). Genotyping and calling of genotypes were performed as described in our previous publications\(^{72,79}\).

For this study cases and controls were identified based on diagnoses given in 2016 or earlier in the Danish Psychiatric Central Research Register\(^{72}\). Cases with ADHD + DBDs had a diagnosis of hyperkinetic conduct disorder (P90.1) or an ADHD diagnosis (ICD-10 P90.0) occurring together with a diagnosis of ODD (ICD-10 F91.3) or conduct disorder (ICD-10 F91.0, F91.1, F91.2, F91.4, 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 P90.0) 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, Genomede (https://genomede.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 and DBDs were included. An overview of the cohorts included in the current analysis and information and diagnosis criteria can be found in Supplementary Data 10. Detailed descriptions of the cohorts can be found elsewhere\(^{44}\). 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 Ricopil\(^{72}\). 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 (\(I_{\text{HET}} < 0.2\)). Genotypes were phased and imputed using SHAPEIT2\(^{45}\) and IMPUTE2\(^{77}\) and the 1000 Genomes Project phase 3 (1KGP)\(^{44}\) as imputation reference panel (the East Asian reference genome was used for...
imputation of the Chinese samples). Trio imputation was done with a case-

Relatedness and population stratification were evaluated using a set of high-

Genetic outliers were excluded based on principal component analyses (PCA) using EIGENSOFT42,43. For

For GSFC, a genetic homogenous sample was defined based on a subsample of

For transancestry genetic risk variants in European and Chinese cohorts, a

The meta-analysis was done as described above including the iPSYCH cohort, the six European PGCC 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 eva-

Secondary GWAS. In order to adjust for the effect of ADHD we did a case-only

We also did an mtCOJO43 analysis to estimate the effect of the top loci for

Gene-based association test. Gene-based association analysis was done using

In addition, we evaluated how much of the variance in the ADHD + DBDs co-

The genetic overlap of ADHD + DBDs with aggression-related phenotypes was evaluated by estimating genetic correlations using LD score regression32 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 18,984 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 individuals44. 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 ADHD+DBDs 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 (13,543 cases and 11,250 controls), showing results consistent with LD score regression ($\rho = 0.97$; SE = 0.06), and not statistically different from one.

Statistical difference between two $\tau$ estimates was calculated using the block jackknife method45 implemented in the LD score regression software46. 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 pseudovalues. 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 \( r_{\text{full}} \) is equal to zero.

**Polygenic score analysis** Case-only polygenic score (PGS) analyses were done using GWAS summary statistics from 22 GWAS related to cognition and education (six phenotypes), personality (nine phenotypes), psychiatric disorders (five phenotypes), and reproductive outcomes (two phenotypes) (detailed list of phenotypes are Supplementary Data 3). Variants with imputation info score < 0.9, MAF < 0.01, missing values, ambiguous and multilocus variants, indels and duplicated identifiers were removed. The remaining variants were LD-clumped using PLINK.\(^{60}\) PGS was estimated at different P-value thresholds in the 22 training datasets (P < 5 × 10^-8, 1 × 10^-7, 1 × 10^-6, 1 × 10^-5, 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 ADHD+orDBDs cases) was 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 select ADHD cases and controls in the IPSYCH cohort were split into five independent samples, then one sample was left out in an ADHID GWAS meta-analysis of IPSYCH data and data from the Psychiatric Genomics Consortium. The results were then used for training and testing for generating PGS in the sample that was left out. This “leave-one-sample out” procedure was repeated until ADHID PGWS 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 \( R^2 \) of a logistic regression including each covariate presented in the GWAS meta-analysis of ADHD + DBDs are available on the IPSYCH website (https://ipsych.dk/en/research/download/).

**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 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.unu.edu/pgc/about-us/people/data-access-committees/). For data access please contact: Ditte Demontis, email: ditte@biomed.au.dk, Anders D. Berglund, 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/download/).

**Code availability** MetaXcan analysis was performed using the R-package metaxcanr (https://github.com/driverx/metaxcan), and GTEx V8 expression prediction models and covariance matrices downloaded from http://predictrdb.org.

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Author contributions

Competing interests
Ditte Demontis has received speaking fee from Takeda. Barbara Franke has received educational speaking fees from Medice. Benjamin M. Neale is a member of the scientific advisory board at Deep Genomics and consultant for Camp4 Therapeutics. Takeda Pharmaceutical and Biogen.

Additional information
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