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Genome-wide analyses of attention deficit hyperactivity disorder identify 27 risk loci, refine the genetic architecture, and implicate several cognitive domains

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Analysis: D.D., G.B.W., G.A., R.W., K.T., L.F., G.V., J.B., B.Z., W.Z., J.D., S.H.M. and T.T.N. **Sample and/or data provider and processing:** D.D, G.B.W., J.G., T.D.A., J.D., F.K.S., J.B.-G., M.B.-H., O.O.G., G.B., K.D., G.S.H., ADHD Working Group of the Psychiatric Genomics Consortium (PGC), iPSYCH-Broad Consortium, E.A., G.E.H., M.N., O.M., D.M.H., P.B.M., M.J.D., H.S., T.W., B.M.N., K.S. and A.D.B. **Writing:** D.D., G.B.W., K.T., G.A., G.V., J.B., H.S. and A.D.B. **Core revision:** D.D., G.B.W., G.A., R.W., K.T., G.V., J.B., S.D., J.M., M.R., F.K.S, D.I.B., M.S.A., N.R.M., D.H., S.E.M., T.Z., V.M.R., S.V.F., H.S., P.R., B.F., B.M.N., K.S. and A.D.B. **Study direction:** D.D. and A.D.B. **Study supervision:** D.D., G.B.W., H.S., P.R., B.F., T.W., B.M.N., K.S. and A.D.B. All authors contributed with critical revision of the manuscript.

COMPETING INTERESTS

B.M.N. currently serves as a member of the scientific advisory board at Deep Genomics and Neumora (previously RBNC) and consultant for Camp4 Therapeutics, Takeda Pharmaceutical, and Biogen. All deCODE affiliated authors are employees of deCODE/Amgen. The remaining authors declare no competing interests.

Code availability

No previously unreported custom computer code or algorithms were used to generate results.

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder with a major genetic component. Here we present a genome-wide association study meta-analysis of ADHD comprising 38,691 individuals with ADHD and 186,843 controls. We identified 27 genome-wide significant loci, highlighting 76 potential risk genes enriched among genes expressed particularly in early brain development. Overall, ADHD genetic risk was associated with several brain-specific neuronal sub-types and midbrain dopaminergic neurons. In exome-sequencing data from 17,896 individuals, we identified an increased load of rare protein-truncating variants in ADHD for a set of risk genes enriched with likely causal common variants, potentially implicating *SORCS3* in ADHD by both common and rare variants. Bivariate Gaussian mixture modeling estimated that 84–98% of ADHD-influencing variants are shared with other psychiatric disorders. Additionally, common variant ADHD risk was associated with impaired complex cognition such as verbal reasoning and a range of executive functions, including attention.

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder, affecting around 5% of children, and persists into adulthood in two-thirds of cases[1,2]. It is characterized by extensive hyperactive, impulsive and/or inattentive behaviors that impair daily functioning. The disorder is associated with multiple adverse outcomes, such as injuries[3], accidents[4], depression[5], substance use disorders[6], aggression[7], premature death[8] and high rate of unemployment[9], and has large societal costs[10–12].

ADHD has a major genetic component, with an estimated twin heritability of 0.74[13]. Despite this, ADHD's complex polygenic architecture makes it difficult to unravel its underlying biological causes. Previously, we discovered the first 12 genome-wide significant loci for ADHD[14] in a genome-wide association study (GWAS) of 20,183 cases and 35,191 controls (here referred to as ADHD2019) that combined the first wave of data from the Danish iPSYCH[15] cohort (iPSYCH1) with 11 ADHD cohorts collected by the Psychiatric Genomics Consortium (PGC). We established the role of common variants in ADHD, explaining around 22% of the variance in the phenotype. The results implicated brain-expressed genes and demonstrated considerable genetic overlap of ADHD with a range of phenotypes, e.g., within psychiatric, cognitive, and metabolic domains. Additionally, a recent cross-disorder GWAS of ADHD and autism[16] has identified shared and differentiating loci and showed that individuals with both ADHD and autism have distinctive patterns of genetic association with other traits compared to those with only a single diagnosis. This highlights that further mapping of the shared genetic risk component with other psychiatric disorders is important for understanding the complexity of the genetics underlying ADHD. Analyses of whole-exome sequencing data have shown that rare variants also contribute to the risk for ADHD[17], especially in mutationally constrained genes.

To better understand the biological mechanisms underlying ADHD, it is fundamental to conduct large genetic studies, as has been demonstrated in other psychiatric disorders[18–20]. Here we present results from an updated GWAS meta-analysis of ADHD, combining data from the newly extended Danish iPSYCH cohort, the Icelandic deCODE cohort and the PGC, almost doubling the number of cases compared with ADHD2019. We fine-map identified risk loci and integrate with functional genomics data to pinpoint potential causal genes and evaluate the burden of rare deleterious variants in top-associated genes. We characterize the polygenic architecture of ADHD and its overlap with other phenotypes by bivariate mixture modeling and perform polygenic score (PGS) analyses to test for association of ADHD-PGS with neurocognitive measures in the Philadelphia Neurodevelopmental Cohort (PNC).

RESULTS

Identification of new ADHD risk loci by GWAS meta-analysis.

We conducted a GWAS meta-analysis based on expanded data from iPSYCH (25,895 cases; 37,148 controls), deCODE genetics (8,281 cases; 137,993 controls) and published data from 10 ADHD cohorts with European ancestry collected by the PGC (4,515 cases; 11,702 controls), resulting in a total sample size of 38,691 individuals with ADHD and 186,843 controls (effective sample size ($n_{\text{eff\_half}}$) = 51,568; cohorts listed in Supplementary Table 1).

The GWAS meta-analysis identified 32 independent lead variants (i.e., with a squared correlation (r^2) < 0.1 between variants) located in 27 genome-wide significant loci (Fig. 1, Table 1, locus plots in Supplementary Data 1, and forest plots in Supplementary Data 2), including 21 novel loci. No statistically significant heterogeneity was observed between cohorts (Supplementary Fig. 1). The three most strongly associated loci ($P < 5 \times 10^{-14}$) were located on chromosome 1 (in and around *PTPRF*), chromosome 5 (downstream of *MEF2C*) and chromosome 11 (downstream of *METTL15*); the latter is a novel ADHD risk locus. Four loci on chromosomes 1, 5, 11, and 20 had secondary genome-wide significant lead variants ($r^2 < 0.1$ between the index variant and the secondary lead variant within a region of 0.5 Mb), but none remained genome-wide significant in analyses conditioning on the index variant using COJO[21] (Supplementary Table 2).

Six of the previously identified 12 loci in the ADHD2019 study[14] were significant in the present study (Table 1), and the remaining six loci demonstrated *P*-values < 8×10^{-4} (Supplementary Table 3). Overall, the direction of association of the top loci (726 loci with $P < 1 \times 10^{-4}$) was consistent with the direction of association in ADHD2019 for all loci but one (Supplementary Table 4).

Genetic correlations among cohorts and SNP-heritability.

Genetic correlation analyses supported a high consistency in the phenotype across cohorts (r_g ranging from 0.82 to 0.93, Supplementary Table 5), and between iPSYCH1 and iPSYCH2 (r_g = 0.97; s.e. = 0.06). None of the genetic correlations were significantly different from 1. LD score regression analysis found an intercept of 1.04 (s.e. = 0.009) and ratio of 0.092 (s.e. = 0.02), the latter indicating that around 90% of the deviation from null, in the distribution of the test statistics, reflects polygenicity (QQ-plot shown in Supplementary Fig. 2). The SNP heritability (h^2_{SNP}) was estimated to 0.14 (s.e. = 0.01), which is lower than the previously reported h^2_{SNP} of 0.22[14]. The h^2_{SNP} for iPSYCH (h^2_{SNP} = 0.23; s.e. = 0.01) was in line with the previous finding, but lower h^2_{SNP} was observed for PGC (h^2_{SNP} = 0.12; s.e. = 0.03) and deCODE (h^2_{SNP} = 0.08; s.e. = 0.014). The difference in h^2_{SNP} was not caused by different sex distributions across cohorts as there were no significant differences in h^2_{SNP} between males and females in the iPSYCH and deCODE cohorts (Supplementary Table 5). Between-cohort heterogeneity in h^2_{SNP} is not unusual and has been observed in other diagnoses such as major depressive disorder[22].

Mapping risk variants to genes and enrichment analyses.

To link identified risk variants to genes, we first identified sets of Bayesian credible variants for each risk locus, with each set most likely (probability > 95%) including a causal variant (Supplementary Table 6). Credible variants were subsequently linked to genes based on genomic position, information about expression quantitative trait loci (eQTLs) and chromatin interaction mapping in human brain tissue as implemented in FUMA[23] (datasets selected are listed in the Supplementary Note). We identified 76 plausible ADHD risk genes (Supplementary Table 7); four of the 76 were mapped by position alone. We found that this set of genes is significantly enriched among genes upregulated during early embryonic brain development (19th post-conceptual week; P_{one_sided} = 0.0008; Supplementary Fig. 3) and highly enriched for genes identified in GWASs of cognition-related phenotypes and

reproduction (Supplementary Fig. 4). The role of the genes in synapses was evaluated using SynGO data[24]; nine genes mapped to SynGO annotations, and genes encoding integral components of the postsynaptic density membrane were borderline significantly enriched ($P = 5.43 \times 10^{-3}$; q-value 0.022; genes *PTPRF*, *SORCS3*, and *DCC*; Supplementary Fig. 5 and Supplementary Table 8). One SynGO-mapped gene was also a part of the upregulated genes during early embryonic brain development (*ARHGAP39*). Additionally, enrichment of the 76 genes in biological pathways was tested using data from 26 databases implemented in Enrichr[25,26]. No pathways showed significant enrichment after Bonferroni correction (database significant findings can be found in Supplementary Table 9). Finally, MAGMA[27] gene-set analysis using gene-based P-values derived from the full GWAS summary statistics (i.e., no preselection of specific genes) did not reveal any significant findings (top gene sets can be found in Supplementary Table 10).

Transcriptome-wide association analysis.

To identify and prioritize ADHD risk genes, we also performed a transcriptome-wide association study (TWAS) of the genetically regulated gene expression using EpiXcan[28] and expression data from the PsychENCODE Consortium[29] on genes as well as isoforms detected in 924 samples from the dorsolateral prefrontal cortex (DLPFC). The TWAS identified 15 genes (Supplementary Table 11) and 18 isoforms (Supplementary Table 12), which together identified 23 distinct genes (Supplementary Fig. 6) with significantly different predicted gene expression levels in ADHD cases compared to controls (after Bonferroni correction for all the 34,646 genes and isoforms tested; Supplementary Fig. 6). Eight of the genes were among the 76 genes mapped by credible variants in FUMA. When using a less stringent correction (false discovery rate < 5%), we identified 237 genes with different predicted expression among cases and controls, of which 19 were also among the 76 prioritized risk genes. The *B4GALT2-205* isoform located in the genome-wide significant locus on chromosome 1 showed the strongest association ($P = 7 \times 10^{-11}$), with lower predicted expression in ADHD compared to controls (Supplementary Fig. 7a). The expression model for *B4GALT2-205* implicated four genome-wide significant variants. The second top gene was *PPP1R16A* ($P = 1.4 \times 10^{-8}$), which showed a predicted under-expression in cases compared to controls. The expression model for this gene implicated one genome-wide significant variant (Supplementary Fig. 7b).

Tissue- and cell type-specific expression of ADHD risk genes.

Gene-based association analysis using MAGMA[27] identified 45 exome-wide significant genes ($P < 2.72 \times 10^{-6}$ (0.05/18,381 genes)) associated with ADHD (Supplementary Table 13). Gene association results across the entire genome were tested for a relationship with tissue-specific gene expression. This showed that brain-expressed genes, and in particular genes expressed in the cortex, are associated with ADHD (Supplementary Fig. 8). This result was supported by LDSC-SEG[30] analysis, showing a significant enrichment in the heritability by variants located in genes specifically expressed in the frontal cortex (Supplementary Table 14).

Next, we examined neuronal cell type-specific gene expression in ADHD using two approaches. First, we tested for enrichment of variants located in cell-specific epigenomic

peaks by intersecting our genetic associations with data from two recent catalogs of the human epigenome that profile major human body cell types[31] as well as brain-specific cell types[32]. Here we found enrichment for genes expressed in major brain neuronal cell types, including both excitatory and inhibitory neurons (Supplementary Fig. 9). Second, we performed cell type-specific analyses in FUMA[33] based on single cell RNA-sequencing data. This revealed a significant association ($P = 0.005$) between ADHD-associated genes and genes expressed in dopaminergic midbrain neurons (Linnarsson midbrain data[34]; Supplementary Fig. 10 and Supplementary Table 15).

Convergence of common and rare variant risk.

To test for convergence of risk conferred by common variants and rare protein-truncating variants (rPTVs), we analyzed whole-exome sequencing data from a subset of the iPSYCH cohort consisting of 8,895 ADHD cases and 9,001 controls. We tested three gene sets: (1) the 76 prioritized risk genes identified by positional and functional annotation, (2) the 45 significant genes in the MAGMA analysis, and (3) 18 genes with at least five credible variants located in the coding region (Supplementary Table 16). While there was no indication of increased burden of rPTVs in the first gene set ($P = 0.39$, OR = 1,30, s.e. = 0.16), the second gene set showed borderline nominal significant enrichment ($P = 0.05$, OR = 1.43, s.e. = 0.18), and the set of genes identified based on credible variants had a significantly increased burden of rPTVs in individuals with ADHD compared to controls ($P = 0.015$, OR = 2.19, s.e. = 0.32). For comparison, there was no enrichment in rare synonymous variants in the third gene set ($P = 0.59$). When evaluating the 18 genes from the “credible gene set” individually, *SORCS3* was nominally significantly ($P = 0.008$; Supplementary Table 16) enriched in rPTVs in ADHD cases when compared to a combined group of iPSYCH controls and gnomAD individuals (non-psychiatric non-Finnish Europeans; $n = 58,121$); this suggests that *SORCS3* might be implicated in ADHD both by common and rare deleterious variants.

Genetic overlap of ADHD with other phenotypes.

The genome-wide genetic correlation (r_g) of ADHD with other phenotypes was estimated using published GWASs (258 phenotypes) and GWASs of UK Biobank data (514 phenotypes), available in LDhub[35]. ADHD showed significant genetic correlation ($P < 2 \times 10^{-4}$) with 56 phenotypes representing domains previously found to have significant genetic correlations with ADHD: cognition (e.g. educational attainment $r_g = -0.55$, s.e. = 0.021), weight/obesity (e.g. body mass index $r_g = 0.27$, s.e. = 0.03), smoking (e.g. smoking initiation $r_g = 0.48$; s.e = 0.07), sleep (e.g. insomnia $r_g = 0.46$, s.e. = 0.05), reproduction (e.g. age at first birth $r_g = -0.65$, s.e. = 0.03) and longevity (e.g. mother’s age at death $r_g = -0.42$, s.e. = 0.07). When considering other neurodevelopmental and psychiatric disorders, autism spectrum disorder (ASD) ($r_g = 0.42$, s.e. = 0.05), schizophrenia (SCZ) ($r_g = 0.17$, s.e. = 0.03), major depressive disorder (MDD) ($r_g = 0.31$, s.e. = 0.07) and cannabis use disorder (CUD) ($r_g = 0.61$, s.e. = 0.04) were significantly correlated with ADHD (Supplementary Table 17). In UK Biobank data, ADHD demonstrated the strongest genetic correlation with a low overall health rating ($r_g = 0.60$, s.e. = 0.2; Supplementary Table 18).

Furthermore, we applied MiXeR[36], which uses univariate and bivariate Gaussian mixture modeling to quantify the actual number of variants that: (1) explain 90% of the SNP heritability of ADHD and (2) overlap between ADHD and other phenotypes representing domains with high genetic correlation with ADHD (psychiatric disorders, smoking behavior, weight, reproduction, and sleep were evaluated). MiXeR considers all variants, i.e., variants with the same and opposite directions of effects. Approximately 7.3K (standard deviation (s.d.) = 324) common variants were found to influence ADHD, which is less than our estimates for SCZ (9.6K; s.d. = 199), MDD (11.7K; s.d. = 345) and ASD (10.3K; s.d. = 1,011), and less than previously reported for bipolar disorder (BD) (8.6K, s.d. = 200)[18].

When considering the number of shared loci as a proportion of the total polygenicity of ADHD, the vast majority of variants influencing ADHD were also estimated to influence the other investigated psychiatric disorders (84%–98%; Fig. 2, Supplementary Fig. 11, and Supplementary Table 19). While the fraction of concordant variants (within the shared part) with ASD and MDD was at the high end (75–76%), it was lower for SCZ (59%). When considering other phenotypes, insomnia demonstrated the smallest overlap with ADHD in terms of actual number of variants (4.5K, s.d. = 1,281; 62% of ADHD variants shared), while almost all variants influencing ADHD also influence educational attainment, age at first birth and smoking (Fig. 2 and Supplementary Table 19). For insomnia and smoking, 83% and 79% of shared variants had concordant directions, respectively, while only 21% and 20% of ADHD risk variants were concordant with educational attainment and age at first birth associated variants, respectively (Supplementary Table 19).

Impact of ADHD polygenic scores on cognitive domains.

Educational attainment is one of the phenotypes with the strongest negative genetic correlation with ADHD, as demonstrated above, and cognitive impairments in ADHD are well described[37]. To further explore how ADHD risk variants affect specific cognitive domains, we assessed the association of ADHD polygenic scores (PGS) with 15 cognitive measures in the Philadelphia Neurodevelopmental Cohort (PNC)[38,39]. This cohort is from the greater Philadelphia area and includes individuals, 8–21 years of age, who received medical care at the Children's Hospital of Philadelphia Network. The subsample of the PNC cohort (v1 release) of 4,973 individuals with European descent was utilized in this study. The Computerized Neurocognitive Battery[40] was used to assess cognitive performance in the study participants. The battery consists of 14 tests in five domains: executive control, episodic memory, complex cognitive processing, social cognition and sensorimotor speed. Additionally, the Wide Range Achievement Test (WRAT-4)[41] was used as a proxy measure for overall IQ[39].

ADHD-PGS was negatively associated with seven neurocognitive measures (Fig. 3), with the strongest association for the WRAT-4 test (beta = −0.09, $P = 1.09 \times 10^{-10}$). ADHD-PGS was associated with measures of executive control (attention: beta = −0.08, $P = 3.94 \times 10^{-8}$; working memory: beta = −0.05, $P = 1.56 \times 10^{-3}$), complex cognition (verbal reasoning: beta = −0.08, $P = 1.31 \times 10^{-10}$; non-verbal reasoning: beta = −0.05, $P = 1.08 \times 10^{-3}$; spatial reasoning: beta = −0.06, $P = 5.15 \times 10^{-5}$) and one measure of episodic memory (facial memory: beta = −0.05, $P = 3.23 \times 10^{-3}$) (Supplementary Table 20). The negative association

of ADHD risk variants with executive functions, especially attention, is in line with the inattention problems often observed in individuals with ADHD.

DISCUSSION

The present study identified 27 genome-wide significant loci in the largest GWAS of ADHD to date. We analyzed around twice as many ADHD cases compared to the ADHD2019[14] study and more than doubled the number of associated loci, indicating that we have passed the inflection point for ADHD with respect to the rate of risk loci discovery.

Six of the 12 previously identified loci were also significant in this study. Even though some previously identified loci demonstrated weaker association here, their associations remained strong, and there was almost complete concordance in the direction of association between top-associated variants in this study and ADHD2019. In GWAS of complex disorders, it is not uncommon for some loci to fluctuate around the significance threshold with increasing sample sizes until they eventually achieve stable significance; this can often be attributed to the "winner's curse" phenomenon, where effect size estimates close to the discovery threshold tend to be overestimated in initial GWAS[42].

We report a lower h^2_{SNP} for ADHD (h^2_{SNP} = 0.14) than estimated previously (h^2_{SNP} = 0.22). This is driven by a lower h^2_{SNP} in the PGC and deCODE cohorts compared to iPSYCH. Different ascertainment and diagnostic strategies and designs among PGC cohorts could decrease the h^2_{SNP}, while a lower effective sample size[43] in Iceland, and thus fewer recent variants, might bias h^2_{SNP} downwards in the deCODE cohort[44].

We refined ADHD's genetic architecture by estimating that around 7.3K (s.d. = 324) common variants can explain 90% of the h^2_{SNP}. This is a higher estimate than reported based on the 2019 ADHD GWAS (5.6K, s.d. = 400)[45], but the current estimate is based on a better fit to the causal mixture model (AIC = 80 vs. AIC = 31 in Hindley et al.[45]). ADHD is often comorbid with other psychiatric disorders[46], with 12–16% of cases also diagnosed with ASD[16,47,48] and around 40% with depression[49], which is also reflected in the genetic correlations reported here and previously[14]. Strikingly, when assessing both concordant and discordant allelic directions, over 90% of ADHD risk variants also seem to influence SCZ and MDD, and 84% influence ASD. This extensive sharing with SCZ, MDD, and ASD is at the same level as observed for SCZ and bipolar disorder[36], which are among the most genetically correlated mental disorders[50]. Notably, for both MDD and ASD, around 75% of the variants shared with ADHD demonstrated concordant direction of association. The large sharing of variants influencing ADHD and other psychiatric disorders, when assessing both concordant and discordant allelic directions, suggests that the disorders are even more intermingled with respect to their common genetic architecture than previously thought based on their overall genetic correlations[36,50]. For common variants, the developmental trajectory towards ADHD might therefore be influenced by variants involved in several psychiatric disorders, but with disorder-specific allelic directions and effect sizes rather than actual ADHD-specific loci.

We also note that almost all variants that influence ADHD overlap with educational attainment[51], and that the vast majority (79%) are associated with decreased educational attainment, consistent with the overall negative genetic correlation. For the models indicating a high number of shared variants (ADHD vs. MDD, SCZ, BMI, educational attainment, age at first birth and smoking), we found support (evaluated using the Akaike Information Criterion[52]) for the best fitting MiXeR models above the "minimal model", which indicate that the data support the existence of a polygenic overlap, beyond the minimal level needed to explain the observed genetic correlations. For ADHD vs. ASD, the model had limited support, and the results should therefore be interpreted with caution.

Fine-mapping of the 27 loci identified credible variants, but only four variants had posterior probabilities greater than 0.5 in all three fine-mapping methods, and none were linked to specific genes based on our functional annotation analyses. Linking the credible variants to genes by integration with functional genomics data identified 76 prioritized risk genes, which were enriched among genes upregulated during early embryonic development and involved in cognitive abilities identified by GWAS of cognitive phenotypes. Among the 76 genes were *PPP1R16A* and *B4GALT2* (mapped by psychENCODE eQTLs; Supplementary Fig. 12a,b), which were also the top-ranking genes in our TWAS of DLPFC expression, both showing a predicted decreased expression in cases compared to controls. These genes have not previously been linked to psychiatric disorders, but both have been linked to educational attainment[51]. The set of risk genes also included *PTPRF*, *SORCS3* and *DCC*, which encode integral components of the postsynaptic density membrane. Involvement of postsynaptic components in the pathology of ADHD has been reported previously[53] and also for SCZ[54]. We also highlight *FOXP1* and *FOXP2*. The association signals were located within the transcribed regions of both genes and had credible variants being eQTLs (*FOXP2*, Supplementary Fig. 12c) or located in chromatin interacting regions (*FOXP1*, Supplementary Fig. 12d) in brain tissue. *FOXP2* was identified in the ADHD2019 study[14] and is also a risk gene for cannabis use disorder[55], while *FOXP1* is a new ADHD locus. Both *FOXP1* and *FOXP2* encode transcription factors that can heterodimerize to regulate transcription in brain tissues[56,57] and have been implicated in speech disorders and intellectual disability[58] by highly penetrant rare variants.

Overall, less than half of the TWAS Bonferroni significant genes overlapped with the 76 candidate risk genes (40% of "TWAS transcript genes"; and 47% of "TWAS genes"; Supplementary Fig. 13). This was not unexpected and could be due to noise in the data and/or that TWAS models are based on expression in adult brains whereas a large proportion of individuals in the GWAS are children. Additionally, eQTLs used to derive TWAS models might not overlap GWAS identified variants as the two types of methods are systematically biased toward identification of different types of variants[59].

We report convergence of common and rare variants in a set of 18 genes defined by location of credible variants. Thirteen of the genes were hit by rPTVs, and eight had a higher load in cases compared to controls, and thus, the signal was not driven by a few genes but by several genes with an increased burden of rPTVs. Of particular note, *SORCS3* seems to be implicated in ADHD by both common and rare variants. Common variants in *SORCS3* show strong pleiotropic effects across several major psychiatric disorders[50], but to our knowledge,

rare variant analyses have not implicated *SORCS3* in psychiatric disorders before. Our results add to the emerging picture of overlap between genes and pathways affected by common and rare variants in psychiatric disorders[54,60–62].

We found that ADHD risk was associated with common variants located in genes significantly expressed in the brain, especially the frontal cortex. We also observed an enrichment of ADHD risk variants in genes expressed in major cell types of the brain, including both excitatory and inhibitory neurons and in midbrain dopaminergic neurons. The findings for frontal cortex and dopamine neurons fit well with the motor, reward and executive function deficits associated with ADHD; the frontal cortex is involved in executive functions including attention and working memory[63], and midbrain dopaminergic neurons are essential for controlling key functions, such as voluntary movement[64] and reward processing[65]. This interpretation is further supported by our ADHD-PGS analyses in PNC, which revealed that common ADHD risk variants impair several domains of cognitive abilities.

The PGS analyses in PNC identified strong association of polygenic ADHD risk with decreased overall IQ (approximated by the WRAT test scores), in line with the high negative genetic correlation of ADHD with educational attainment and the observation that 79% of all ADHD risk variants are associated with decreased educational attainment. Interestingly, we found that ADHD-PGS associates with decreased attention, which is a key ADHD symptom, and with impairments in measures of other cognitive traits such as working memory. Smaller studies have analyzed the impact of ADHD-PGS on executive functions with mixed results[66–69]. This study robustly identifies specific cognitive domains impacted by ADHD-PGS, and our results support ADHD-PGS being negatively associated with neurocognitive performance.

In summary, we identified new ADHD risk loci, highlighted candidate causal genes, and implicated genes expressed in frontal cortex and several brain specific neuronal subtypes in ADHD. Our analyses revealed ADHD to be highly polygenic, influenced by thousands of variants, of which the vast majority also influence other psychiatric disorders with concordant or discordant effects. Additionally, we demonstrated that common variant ADHD risk has an impairing impact on a range of executive functions. Overall, the results advance our understanding of the underlying biology of ADHD and reveal novel aspects of ADHD's polygenic architecture, its relationship with other phenotypes, and its impact on cognitive domains.

METHODS

The study was approved by the local scientific ethics committees and IRBs. The iPSYCH study was approved by the Scientific Ethics Committee in the Central Denmark Region (Case No 1-10-72-287-12) and the Danish Data Protection Agency. In accordance with Danish legislation, the Danish Scientific Ethics Committee has, for this study, waived the need for specific informed consent in biomedical research based on existing biobanks. This deCODE study was approved by the National Bioethics Committee of Iceland (VSN 15-047) and all participants gave informed consent.

Samples, quality control and imputation.

iPSYCH.—The iPSYCH[15,70] cohort consists of 129,950 genotyped individuals, among which 85,891 are cases diagnosed with at least one of six mental disorders (i.e., ADHD, SCZ, BD, MDD, ASD, post-partum disorder) and the remaining are population-based controls. Samples were selected from a baseline birth cohort comprising all singletons born in Denmark between May 1, 1981, and December 31, 2008, who were residents in Denmark on their first birthday and who have a known mother (n = 1,657,449). ADHD cases were diagnosed by psychiatrists according to the ICD10 criteria (F90.0, F90.1, F98.8 diagnosis codes) identified using the Danish Psychiatric Central Research Register[71] and the Danish National Patient register[72]. Diagnoses were given in 2016 or earlier for individuals at least 1 year old. Controls were randomly selected from the same nationwide birth cohort and not diagnosed with ADHD.

Detailed information on genotyping, imputation and quality control can be found in the Supplementary Note. After QC, the iPSYCH1 ADHD sample included 38,899 individuals and iPSYCH2 included 24,144 individuals.

deCODE.—The deCODE cohort consisted of 8,281 individuals with ADHD. These were either individuals with a clinical diagnosis of ADHD (n = 5,583) according to the ICD10 criteria (ICD10-F90, F90.1, F98.8) or individuals that have been prescribed medication specific for ADHD symptoms (ATC-NA06BA, mostly methylphenidate) (n = 2,698). The control sample did not contain individuals with a diagnosis of SCZ, BD, ASD or self-reported ADHD symptoms or diagnosis. All participants who donated samples gave informed consent. Information about genotyping, QC and evaluation of potential genetic heterogeneity between individuals identified based on diagnosis codes and medication can be found in the Supplementary Note.

PGC cohorts.—We used summary statistics from the 10 PGC cohorts with European ancestry generated as a part of our previous GWAS meta-analysis of ADHD. Detailed information about cohort design, genotyping, QC, and imputation can be found in Demontis et al.[14].

GWAS meta-analysis of ADHD.

GWASs were performed separately for iPSYCH1 (17,019 cases and 21,880 controls) and iPSYCH2 (8,876 cases and 15,268 controls) using dosages for imputed genotypes and additive logistic regression with the first 10 PCs (from the final PCAs) as covariates using PLINK v1.9.

GWAS of deCODE samples (8,281 ADHD cases; 137,993 controls) was done using dosage data and logistic regression with sex, year of birth, and county of origin as covariates. To account for inflation due to population stratification and cryptic relatedness, test statistics were divided by an inflation factor (lambda = 1.23) estimated from LD score regression as done previously[55]. Findings from analyses of the genetic structure of the Icelandic population by Price et al.[73] support that lambda correction will ensure proper correction without false positives. Subsequently alleles were converted to match HRC alleles.

For the PGC cohorts, we used GWAS summary statistics for each of the 10 European PGC cohorts generated as a part of our previous GWAS meta-analysis[14].

See Supplementary Note for sensitivity analyses related to the impact of using sex and age as covariates in the analyses. See Supplementary Figure 14 for the impact of including or excluding sex as covariate in GWAS of iPSYCH data.

Summary statistics from GWAS of the individual cohorts, containing variants with imputation quality (INFO score) > 0.8 and minor allele frequency > 0.01, were meta-analyzed with a fixed effects standard error weighted meta-analysis using METAL (version 2011-03-25)[74]. Only variants supported by an effective sample size greater than 60% were retained in the final summary statistics (6,774,224 variants).

Concordance in the direction of associations in the present GWAS with associations in the ADHD2019 data was evaluated by a sign-test at different *P*-value thresholds (see thresholds in Supplementary Table 4).

Conditional analysis.

We identified potentially independent genome-wide significant lead variants for four loci located on chromosome 1 (two secondary lead variants), 5, 11 and 20. To evaluate if these variants were independent from the lead variants, we performed association analyses of the secondary variants while conditioning on the index variant in the locus using COJO as implemented in GCTA[21].

Identification of sets of credible variants.

To identify sets of causal variants, we fine-mapped each of the 27 genome-wide loci using three fine-mapping tools, FINEMAP v. 1.3.1 (ref. [75]), PAINTOR v.3.0 (ref. [76]) and CAVIARBF v.0.2.1 (ref. [77]), using CAUSALdb-finemapping-pip downloaded from https://github.com/mulinlab/CAUSALdb-finemapping-pip[78]. Since no secondary lead variants remained genome-wide significant after conditional analyses, one causal variant was assumed per locus. Variants located in a region of 1 Mb around index variants were included in the analyses. We used a threshold of 95% for the total posterior probability of the variants included in the credible sets, and only variants claimed to be within the set by all three methods were included in the final credible set for each locus.

Genetic correlations among cohorts and SNP heritability.

SNP heritability (h^2_{SNP}) and pair-wise genetic correlation among the cohorts were calculated using LD score regression[79] analysis of summary statistics from GWAS of deCODE samples, meta-analysis of iPSYCH1+iPSYCH2 and meta-analysis of the 10 PGC cohorts (applying the same approach as described for the meta-analysis of all cohorts). Conversion of h^2_{SNP} estimates from observed scale to the liability scale was done using a population prevalence of 5%. Test for significant differences in h^2_{SNP} between cohorts was done using a *Z*-test.

Mapping of risk genes, enrichment and pathway analyses.

To link identified risk variants to genes, we used the set of credible variants (identified as described above) for each locus and linked variants to genes based on genomic position and functional annotations in FUMA[23]. Protein coding genes were mapped if they were located with a distance of 10 kb upstream or downstream of the index variants or if a credible variant was annotated to the gene based on eQTL data or chromatin interaction data from human brain (datasets used are listed in the Supplementary Note). The mapping linked credible variants to 76 ADHD prioritized risk genes. These genes were used in gene-set enrichment analyses to evaluate if the candidate genes were enriched among (1) genes differentially expressed in specific brain tissues, (2) genes differentially expressed at specific brain developmental stages, (3) genes encoding proteins involved in synapses and (4) genes encoding proteins in specific biological pathways. We corrected for multiple testing separately for each of these hypotheses. The first two aims were addressed by performing enrichment analyses in the GENE2FUNC module in FUMA. Enrichment of ADHD risk genes among predefined sets of differentially expressed genes in GTEx (54 tissue types) and BrainSpan (29 different ages of samples and 11 general developmental stages) data using hypergeometric test, and protein-coding genes were chosen as background genes.

The third aim was addressed using SynGO[24] (dataset version: 20210225) to test for enrichment among the 76 risk genes for genes involved in synaptic processes and locations. We analyzed for enrichment in two subsets: “biological process” (201 gene sets) and “cellular component” (92 gene sets). We controlled using a background set of “brain expressed” genes provided by the SynGo platform (defined as ‘expressed in any GTEx v7 brain tissues’) containing 18,035 unique genes, of which 1,225 overlap with SynGO annotated genes. For each ontology term, a one-sided Fisher exact test was performed to compare the list of ADHD risk genes and the selected background set. To find enriched terms within the entire SynGO ontology, the most specific term is selected where each ‘gene cluster’ (unique set of genes) is found and then multiple testing correction is applied using False Discovery Rate (FDR) on the subset of terms that contain these ‘gene clusters’. Only ontology terms with gene sets with a minimum of three genes were included in the enrichment analysis.

The fourth aim was addressed by testing if the 76 genes were enriched in pathways/gene sets using Enrichr[25,26] and its implemented databases (26 databases). Only pathways enriched with more than two genes were considered. We took a conservative approach and only considered pathways to be significant if the within-database adjusted *P*-value was smaller than 0.002 (0.05/26 databases evaluated). After correction for the number of databases, no significantly enriched pathways were identified.

We also tested for enrichment among the 76 genes of genes reported from the GWAS catalog (2019) and UK Biobank GWASs (v1) and used https://appyters.maayanlab.cloud/Enrichr_Manhattan_Plot/ to visualize the results.

Finally, we conducted pathway enrichment analysis using results from the full GWAS meta-analysis (i.e., no preselection of genes) by performing MAGMA[27] gene-set analysis in FUMA (see details in the Supplementary Note).

Transcriptomic imputation model construction and TWAS.

Transcriptomic imputation models were constructed as previously described[28] for dorso-lateral prefrontal cortex (DLPFC) transcript levels[80]. The genetic dataset of the PsychENCODE cohort was uniformly processed for quality control (QC) steps before genotype imputation. The analysis was restricted to samples with European ancestry as previously described[28]. Genotypes were imputed using the University of Michigan server[81] with the Haplotype Reference Consortium (HRC) reference panel[82]. Gene expression information (both at the level of gene and transcript) was derived from RNA-seq counts which were adjusted for known and hidden confounds, followed by quantile normalization[80]. For the construction of the transcriptomic imputation models, we used EpiXcan[28], an elastic net-based method, which weighs SNPs based on available epigenetic annotation information[83]. We performed the transcript-trait association analysis for ADHD as previously described[28]. Briefly, we applied the S-PrediXcan method[28] to integrate the ADHD GWAS meta-analysis summary statistics and the transcriptomic imputation models constructed above to obtain association results at both the level of genes and transcripts.

Gene-based association and tissue-specific gene expression.

We used MAGMA v1.08 implemented in FUMA v1.3.6a[23] to perform gene-based association analysis using the full summary statistics from the GWAS meta-analysis. Genome-wide significance was assessed through Bonferroni correction for the number of genes tested ($P = 0.05/18381 = 2.72 \times 10^{-6}$).

The relationships between tissue-specific gene expression profiles and ADHD-gene associations were tested using MAGMA gene-property analysis of expression data from GTEx (54 tissue types) and BrainSpan (29 brain samples at different ages) available in FUMA (see Supplementary Note for datasets selected).

Enrichment in h^2_{SNP} of ADHD-associated variants located in or close to genes expressed in specific brain regions was estimated using LDSC-SEG[30]. Annotations indicating specific expression in 13 brain regions from the GTEx gene expression database were downloaded from https://alkesgroup.broadinstitute.org/LDSCORE/LDSC_SEG_ldscores/.

Cell type-specific expression of ADHD risk genes.

We tested for enrichment in the ADHD h^2_{SNP} of variants located in cell type-specific epigenetic peaks by examining the overlap of common genetic risk variants with open chromatin from a DHS (DNase I hypersensitive sites) study profiling major human cell types[31] and an scATAC-seq (single-cell assay for transposase accessible chromatin)[32] study using an LD-score partitioned heritability approach[84]. All regions of open chromatin were extended by 500 bp in either direction. The broad MHC region (hg19 chr6:25–35Mb) was excluded due to its extensive and complex LD structure, but otherwise default parameters

were used for the algorithm. We applied Bonferroni correction (correcting for 23 cell types), and results below $P = 0.0022$ were considered significant.

Additionally, we performed cell type-specific analyses implemented in FUMA, using data from 13 single-cell RNA sequencing datasets from human brain. The method is described in detail in Watanabe et al.[33]. Datasets used and a short summary of the method can be found in the Supplementary Note).

Overlap of common ADHD risk variants with rare protein-truncating variants (rPTVs).

We analyzed the overlap of common variants with rPTVs in a subset of iPSYCH samples that have also been whole exome sequenced. A major part of the data (Pilot 1, Wave 1, Wave 2) was also included in the recent study by Satterstrom et al.[17], and the same quality control procedure was applied in this study. Description of whole-exome sequencing procedure, QC and annotation can be found in the Supplementary Note. Variants were defined as PTVs if they were annotated as having large effects on gene function (nonsense variant, frameshift, splice site). We defined a variant as being rare if it had an allele count of five or less across the combination of the full iPSYCH exome-sequencing dataset ($n = 28,448$) and non-Finnish Europeans in the nonpsychiatric gnomAD exome database ($n = 44,779$).

We tested for increased burden of rPTVs in ADHD compared to controls in three gene sets: (1) the 76 genes linked to credible variants based on position and functional genomic data, (2) the 45 exome-wide significant genes identified in MAGMA analysis, and (3) genes with at least five credible variants within the coding regions. The requirement of five credible variants was chosen to prioritize the most likely causal genes. This threshold excluded eight genes located in the same locus covering a broad LD region on chromosome 3 (Supplementary Data 1; page 25). Additionally, two other genes with less than five credible variants were excluded located in two other loci on chromosome 3.

The burden of rPTVs and rare synonymous (rSYNs) in cases compared to controls was tested for the three gene sets with logistic regression corrected using the following covariates: birth year, sex, first ten principal components, number of rSYN, percentage of target with coverage > 20x, mean read depth at sites within the exome target passing VQSR, total number of variants, sequencing wave.

Only significant enrichment in the set of 18 genes identified based on credible variants was found. We therefore looked specifically into these genes to identify whether the signal was driven by specific genes. rPTVs were found in 13 of the genes, and eight of these genes had more rPTVs in cases than controls when looking at raw counts (Supplementary Table 16). We performed gene-based burden test using EPACTS (https://genome.sph.umich.edu/wiki/EPACTS) and a logistic Wald test (correcting using the covariates as described above). Additionally, in order to increase power to detect an increased burden of rPTVs at the gene level in ADHD cases, we combined iPSYCH controls with information about rPTVs in gnomAD (non-Finnish European individuals), done as described previously[17]. We performed these gene-based tests using Fisher's exact test, and only the following genes were considered: (1) genes with a higher number rSYN in gnomAD controls compared to

iPSYCH cases, and (2) genes with a higher rate of rPTVs in cases compared to controls in the iPSYCH data.

Genetic overlap with other phenotypes.

We estimated genetic correlations of ADHD with other phenotypes in LDhub[35] (published GWASs: 255 phenotypes; UK Biobank GWASs: 514 phenotypes). Additionally, genetic correlations with three phenotypes not available in LDhub (cannabis use disorder[55], smoking initiation[85] and education attainment[51]) were estimated locally using LD score regression[79].

We applied MiXeR[36] to our ADHD GWAS summary statistics and GWAS from a selection of complex traits showing high genetic correlation with ADHD: ASD[86], SCZ[54], BMI[87], educational attainmet[88], age at first birth[89], smoking initiation[85], insomnia[90] and a new GWAS meta-analysis of depression including 371,184 cases and 978,703 controls[91] (Supplementary Table 19) to quantify (i) the number of variants influencing each trait and (ii) the genetic overlap between ADHD and each of the other traits. We used MiXeR with default settings (https://github.com/precimed/mixer) in a two-step process. First, we ran a univariate model for each trait to estimate the number of common variants having a non-zero genetic additive impact on the phenotype. The univariate model generates estimates of “polygenicity” (i.e., the proportion of non-null variants) and “discoverability” (i.e., the variance of effect sizes of non-null SNPs). Second, the variance estimates from the univariate step were used to run a bivariate model in a pairwise fashion (i.e. ADHD vs. each of the other traits), which produced estimates of SNPs with a specific effect on the first or on the second trait, and SNPs with a non-zero effect on both traits (for details on the method see also ref. [18] and Supplementary Note). The models were evaluated by the Akaike Information Criterion[52] (AIC) and illustrated with modeled versus observed conditional quantile-quantile (Q-Q) plots (Supplementary Fig. 11). The AIC values can be found in Supplementary Table 19.

Polygenic score (PGS) analysis of cognitive measures in PNC.

PGS analysis was performed on 4,973 individuals of European ancestry from the Philadelphia Neurodevelopmental Cohort (PNC), ages 8–21. Information about imputation and QC of the PNC data can be found in the Supplementary Note.

The software PRS-CS[92] was used to process ADHD GWAS summary statistics and assign per-allele posterior SNP effect sizes. A European LD reference panel generated from the 1000 Genomes Project data (https://github.com/getian107/PRScs) was utilized. The following default settings were used for PRS-CS: parameter a in the γ-γ prior = 1, parameter b in the γ-γ prior = 0.5, MCMC iterations = 1000, number of burn-in iterations = 500, and thinning of the Markov chain factor = 5. Additionally, the global shrinkage parameter phi was determined using a fully Bayesian method. Plink v2.0[93] was then used to calculate individual-level ADHD PGS. Linear regression was used to test the association between ADHD PGS and neurocognitive phenotypes measured in the PNC. Age (at time of neurocognitive testing), age^2, genotyping batch, sex, and the first 10 MDS dimensions were used as covariates. The neurocognitive measures were obtained using the Computerized Neurocognitive Battery (CNB), which consists of 14 tests in 5 domains: executive control,

episodic memory, complex cognitive processing, social cognition, and sensorimotor speed. The battery has been described in detail elsewhere[40]. Additionally, association of ADHD-PGS with results from the Wide Range Achievement Test (WRAT-4)[41] were analyzed. See Supplementary Note regarding transformation of the CNB measures.

The total variance explained by ADHD-PGS and model covariates for each neurocognitive phenotype was reported using Adjusted R^2. Additionally, the variance explained by ADHD-PGS was calculated in R using a variance partitioning tool (https://github.com/GabrielHoffman/misc_vp/blob/master/calcVarPart.R). Reported *P*-values were Bonferroni-adjusted to account for the number of independent tests performed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Summary statistics from the ADHD GWAS meta-analysis are available for download at the PGC website (https://www.med.unc.edu/pgc/download-results/). 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 (GenomeDK; https://

genome.au.dk) as the data are protected by Danish legislation. For data access and correspondence, please contact Ditte Demontis (ditte@biomed.au.dk) or Anders D. Børglum (anders@biomed.au.dk).

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REFERENCES

1. Faraone SV et al. Attention-deficit/hyperactivity disorder. Nature Reviews Disease Primers, 15020 (2015).
2. Franke B et al. The genetics of attention deficit/hyperactivity disorder in adults, a review. Mol Psychiatry 17, 960–87 (2012). [PubMed: 22105624]

3. Dalsgaard S, Leckman JF, Mortensen PB, Nielsen HS & Simonsen M Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. Lancet Psychiatry 2, 702–9 (2015). [PubMed: 26249301]
4. Chang Z, Lichtenstein P, D'Onofrio BM, Sjolander A & Larsson H Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. JAMA Psychiatry 71, 319–25 (2014). [PubMed: 24477798]
5. Babinski DE, Neely KA, Ba DM & Liu G Depression and Suicidal Behavior in Young Adult Men and Women With ADHD: Evidence From Claims Data. J Clin Psychiatry 81, 19m13130 (2020).
6. Capusan AJ, Bendtsen P, Marteinsdottir I & Larsson H Comorbidity of Adult ADHD and Its Subtypes With Substance Use Disorder in a Large Population-Based Epidemiological Study. J Atten Disord 23, 1416–1426 (2019). [PubMed: 26838558]
7. Boomsma DI, van Beijsterveldt T, Odintsova VV, Neale MC & Dolan CV Genetically Informed Regression Analysis: Application to Aggression Prediction by Inattention and Hyperactivity in Children and Adults. Behav Genet 51, 250–263 (2021). [PubMed: 33259025]
8. Dalsgaard S, Ostergaard SD, Leckman JF, Mortensen PB & Pedersen MG Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. Lancet 385, 2190–6 (2015). [PubMed: 25726514]
9. Jangmo A et al. Attention-deficit/hyperactivity disorder and occupational outcomes: The role of educational attainment, comorbid developmental disorders, and intellectual disability. PLoS One 16, e0247724 (2021). [PubMed: 33730071]
10. Zhao X et al. Family Burden of Raising a Child with ADHD. J Abnorm Child Psychol 47, 1327–1338 (2019). [PubMed: 30796648]
11. Le HH et al. Economic impact of childhood/adolescent ADHD in a European setting: the Netherlands as a reference case. Eur Child Adolesc Psychiatry 23, 587–98 (2014). [PubMed: 24166532]
12. Libutzki B et al. Direct medical costs of ADHD and its comorbid conditions on basis of a claims data analysis. Eur Psychiatry 58, 38–44 (2019). [PubMed: 30802682]
13. Faraone SV & Larsson H Genetics of attention deficit hyperactivity disorder. Mol Psychiatry 24, 562–575 (2019). [PubMed: 29892054]
14. Demontis D et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 51, 63–75 (2019). [PubMed: 30478444]
15. Pedersen CB et al. The iPSYCH2012 case-cohort sample: new directions for unravelling genetic and environmental architectures of severe mental disorders. Mol Psychiatry 23, 6–14 (2018). [PubMed: 28924187]
16. Mattheisen M et al. Identification of shared and differentiating genetic architecture for autism spectrum disorder, attention-deficit hyperactivity disorder and case subgroups. Nat. Genet. 54, 1470–1478 (2022). [PubMed: 36163277]
17. Satterstrom FK et al. Autism spectrum disorder and attention deficit hyperactivity disorder have a similar burden of rare protein-truncating variants. Nat Neurosci 22, 1961–1965 (2019). [PubMed: 31768057]
18. Mullins N et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet 53, 817–829 (2021). [PubMed: 34002096]
19. Howard DM et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci 22, 343–352 (2019). [PubMed: 30718901]
20. Pardinas AF et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat Genet 50, 381–389 (2018). [PubMed: 29483656]
21. Yang J, Lee SH, Goddard ME & Visscher PM GCTA: a tool for genome-wide complex trait analysis. Am J Hum Genet 88, 76–82 (2011). [PubMed: 21167468]
22. Trzaskowski M et al. Quantifying between-cohort and between-sex genetic heterogeneity in major depressive disorder. Am J Med Genet B Neuropsychiatr Genet 180, 439–447 (2019). [PubMed: 30708398]

23. Watanabe K, Taskesen E, van Bochoven A & Posthuma D Functional mapping and annotation of genetic associations with FUMA. Nat Commun 8, 1826 (2017). [PubMed: 29184056]
24. Koopmans F et al. SynGO: An Evidence-Based, Expert-Curated Knowledge Base for the Synapse. Neuron 103, 217–234 e4 (2019). [PubMed: 31171447]
25. Xie Z et al. Gene Set Knowledge Discovery with Enrichr. Curr Protoc 1, e90 (2021). [PubMed: 33780170]
26. Kuleshov MV et al. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. Nucleic Acids Res 44, W90–7 (2016). [PubMed: 27141961]
27. de Leeuw CA, Mooij JM, Heskes T & Posthuma D MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol 11, e1004219 (2015). [PubMed: 25885710]
28. Zhang W et al. Integrative transcriptome imputation reveals tissue-specific and shared biological mechanisms mediating susceptibility to complex traits. Nat Commun 10, 3834 (2019). [PubMed: 31444360]
29. Wang D et al. Comprehensive functional genomic resource and integrative model for the human brain. Science 362, eaat8464 (2018). [PubMed: 30545857]
30. Finucane HK et al. Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. Nat Genet 50, 621–629 (2018). [PubMed: 29632380]
31. Meuleman W et al. Index and biological spectrum of human DNase I hypersensitive sites. Nature 584, 244–251 (2020). [PubMed: 32728217]
32. Corces MR et al. Single-cell epigenomic analyses implicate candidate causal variants at inherited risk loci for Alzheimer's and Parkinson's diseases. Nat Genet 52, 1158–1168 (2020). [PubMed: 33106633]
33. Watanabe K, Umicevic Mirkov M, de Leeuw CA, van den Heuvel MP & Posthuma D Genetic mapping of cell type specificity for complex traits. Nat Commun 10, 3222 (2019). [PubMed: 31324783]
34. La Manno G et al. Molecular Diversity of Midbrain Development in Mouse, Human, and Stem Cells. Cell 167, 566–580.e19 (2016). [PubMed: 27716510]
35. Zheng J et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics 33, 272–279 (2017). [PubMed: 27663502]
36. Frei O et al. Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. Nat Commun 10, 2417 (2019). [PubMed: 31160569]
37. Franke B et al. Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. Eur Neuropsychopharmacol 28, 1059–1088 (2018). [PubMed: 30195575]
38. Satterthwaite TD et al. Neuroimaging of the Philadelphia neurodevelopmental cohort. Neuroimage 86, 544–53 (2014). [PubMed: 23921101]
39. Calkins ME et al. The Philadelphia Neurodevelopmental Cohort: constructing a deep phenotyping collaborative. J Child Psychol Psychiatry 56, 1356–1369 (2015). [PubMed: 25858255]
40. Gur RC et al. Age group and sex differences in performance on a computerized neurocognitive battery in children age 8–21. Neuropsychology 26, 251–265 (2012). [PubMed: 22251308]
41. Wilkinson GS & Robertson GJ Wide range achievement test (WRAT4). Lutz, FL: Psychological Assessment Resources (2006).
42. Uffelmann E et al. Genome-wide association studies. Nature Reviews Methods Primers 1, 59 (2021).
43. Bataillon T et al. The effective size of the Icelandic population and the prospects for LD mapping: inference from unphased microsatellite markers. Eur J Hum Genet 14, 1044–53 (2006). [PubMed: 16736029]
44. Gazal S et al. Linkage disequilibrium-dependent architecture of human complex traits shows action of negative selection. Nat Genet 49, 1421–1427 (2017). [PubMed: 28892061]
45. Hindley G et al. The shared genetic basis of mood instability and psychiatric disorders: A cross-trait genome-wide association analysis. Am J Med Genet B Neuropsychiatr Genet 189, 207–218 (2022). [PubMed: 35841185]

46. Plana-Ripoll O et al. Exploring Comorbidity Within Mental Disorders Among a Danish National Population. JAMA Psychiatry 76, 259–270 (2019). [PubMed: 30649197]
47. Zablotsky B, Bramlett MD & Blumberg SJ The Co-Occurrence of Autism Spectrum Disorder in Children With ADHD. J Atten Disord 24, 94–103 (2020). [PubMed: 28614965]
48. Jensen CM & Steinhausen HC Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. Atten Defic Hyperact Disord 7, 27–38 (2015). [PubMed: 24942707]
49. Chen Q et al. Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-sectional study. PLoS One 13, e0204516 (2018). [PubMed: 30256837]
50. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. Cell 179, 1469–1482.e11 (2019). [PubMed: 31835028]
51. Lee JJ et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat Genet 50, 1112–1121 (2018). [PubMed: 30038396]
52. Akaike H A new look at the statistical model identification. IEE Transactions on Automatic Controls 19, 716–723 (1974).
53. Yao X et al. Integrative analysis of genome-wide association studies identifies novel loci associated with neuropsychiatric disorders. Transl Psychiatry 11, 69 (2021). [PubMed: 33479212]
54. Trubetskoy V et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604, 502–508 (2022). [PubMed: 35396580]
55. Johnson EC et al. A large-scale genome-wide association study meta-analysis of cannabis use disorder. Lancet Psychiatry 7, 1032–1045 (2020). [PubMed: 33096046]
56. Araujo DJ et al. FoxP1 orchestration of ASD-relevant signaling pathways in the striatum. Genes Dev 29, 2081–96 (2015). [PubMed: 26494785]
57. Fong WL, Kuo HY, Wu HL, Chen SY & Liu FC Differential and Overlapping Pattern of Foxp1 and Foxp2 Expression in the Striatum of Adult Mouse Brain. Neuroscience 388, 214–223 (2018). [PubMed: 30031127]
58. Sollis E et al. Equivalent missense variant in the FOXP2 and FOXP1 transcription factors causes distinct neurodevelopmental disorders. Hum Mutat 38, 1542–1554 (2017). [PubMed: 28741757]
59. Mostafavi H, Spence JP, Naqvi S & Pritchard JK Limited overlap of eQTLs and GWAS hits due to systematic differences in discovery. bioRxiv (2022).
60. Satterstrom FK et al. Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. Cell 180, 568–584.e23 (2020). [PubMed: 31981491]
61. Singh T et al. Rare coding variants in ten genes confer substantial risk for schizophrenia. Nature 604, 509–516 (2022). [PubMed: 35396579]
62. Sazonovs A et al. Large-scale sequencing identifies multiple genes and rare variants associated with Crohn's disease susceptibility. Nat. Genet. 54, 1275–1283 (2021).
63. Bahmani Z et al. Prefrontal Contributions to Attention and Working Memory. Curr Top Behav Neurosci 41, 129–153 (2019). [PubMed: 30739308]
64. Sonne J, Reddy V & Beato MR Neuroanatomy, Substantia Nigra. in StatPearls (Treasure Island (FL), 2021).
65. Morales M & Margolis EB Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. Nat Rev Neurosci 18, 73–85 (2017). [PubMed: 28053327]
66. Chang S, Yang L, Wang Y & Faraone SV Shared polygenic risk for ADHD, executive dysfunction and other psychiatric disorders. Transl Psychiatry 10, 182 (2020). [PubMed: 32518222]
67. Nigg JT et al. Working Memory and Vigilance as Multivariate Endophenotypes Related to Common Genetic Risk for Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry 57, 175–182 (2018). [PubMed: 29496126]
68. Aguilar-Lacasana S et al. Polygenic risk for ADHD and ASD and their relation with cognitive measures in school children. Psychol Med. 52, 1356–1364 (2022). [PubMed: 32924895]

69. Martin J, Hamshere ML, Stergiakouli E, O'Donovan MC & Thapar A Neurocognitive abilities in the general population and composite genetic risk scores for attention-deficit hyperactivity disorder. J Child Psychol Psychiatry 56, 648–56 (2015). [PubMed: 25280069]

Methods-only references

70. Bybjerg-Grauholm J et al. The iPSYCH2015 Case-Cohort sample: updated directions for unravelling genetic and environmental architectures of severe mental disorders. medRxiv (2020).

71. Mors O, Perto GP & Mortensen PB The Danish Psychiatric Central Research Register. Scand J Public Health 39, 54–7 (2011). [PubMed: 21775352]

72. Lynge E, Sandegaard JL & Rebolj M The Danish National Patient Register. Scand J Public Health 39, 30–3 (2011). [PubMed: 21775347]

73. Price AL et al. The impact of divergence time on the nature of population structure: an example from Iceland. PLoS Genet 5, e1000505 (2009). [PubMed: 19503599]

74. Willer CJ, Li Y & Abecasis GR METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 26, 2190–1 (2010). [PubMed: 20616382]

75. Benner C et al. FINEMAP: efficient variable selection using summary data from genome-wide association studies. Bioinformatics 32, 1493–501 (2016). [PubMed: 26773131]

76. Greenbaum J & Deng HW A Statistical Approach to Fine Mapping for the Identification of Potential Causal Variants Related to Bone Mineral Density. J Bone Miner Res 32, 1651–1658 (2017). [PubMed: 28425624]

77. Chen W et al. Fine Mapping Causal Variants with an Approximate Bayesian Method Using Marginal Test Statistics. Genetics 200, 719–36 (2015). [PubMed: 25948564]

78. Wang J et al. CAUSALdb: a database for disease/trait causal variants identified using summary statistics of genome-wide association studies. Nucleic Acids Res 48, D807–D816 (2020). [PubMed: 31691819]

79. Bulik-Sullivan BK et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 47, 291–5 (2015). [PubMed: 25642630]

80. Gandal MJ et al. Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. Science 362, eaat8127 (2018). [PubMed: 30545856]

81. Das S et al. Next-generation genotype imputation service and methods. Nat Genet 48, 1284–1287 (2016). [PubMed: 27571263]

82. McCarthy S et al. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet 48, 1279–83 (2016). [PubMed: 27548312]

83. Roadmap Epigenomics Consortium et al. Integrative analysis of 111 reference human epigenomes. Nature 518, 317–30 (2015). [PubMed: 25693563]

84. Finucane HK et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. Nat Genet 47, 1228–35 (2015). [PubMed: 26414678]

85. Liu M et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat Genet 51, 237–244 (2019). [PubMed: 30643251]

86. Grove J et al. Identification of common genetic risk variants for autism spectrum disorder. Nat Genet 51, 431–444 (2019). [PubMed: 30804558]

87. Yengo L et al. Meta-analysis of genome-wide association studies for height and body mass index in approximately 700000 individuals of European ancestry. Hum Mol Genet 27, 3641–3649 (2018). [PubMed: 30124842]

88. Okbay A et al. Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. Nat Genet 54, 437–449 (2022). [PubMed: 35361970]

89. Mills MC et al. Identification of 371 genetic variants for age at first sex and birth linked to externalising behaviour. Nat Hum Behav 5, 1717–1730 (2021). [PubMed: 34211149]

90. Watanabe K et al. Genome-wide meta-analysis of insomnia prioritizes genes associated with metabolic and psychiatric pathways. Nat. Genet. 54, 1125–1132 (2022). [PubMed: 35835914]

91. Als TD et al. Identification of 64 new risk loci for major depression, refinement of the genetic architecture and risk prediction of recurrence and comorbidities. medRxiv (2022).

92. Ge T, Chen CY, Ni Y, Feng YA & Smoller JW Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun 10, 1776 (2019). [PubMed: 30992449]

93. Chang CC et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 4, 7 (2015). [PubMed: 25722852]

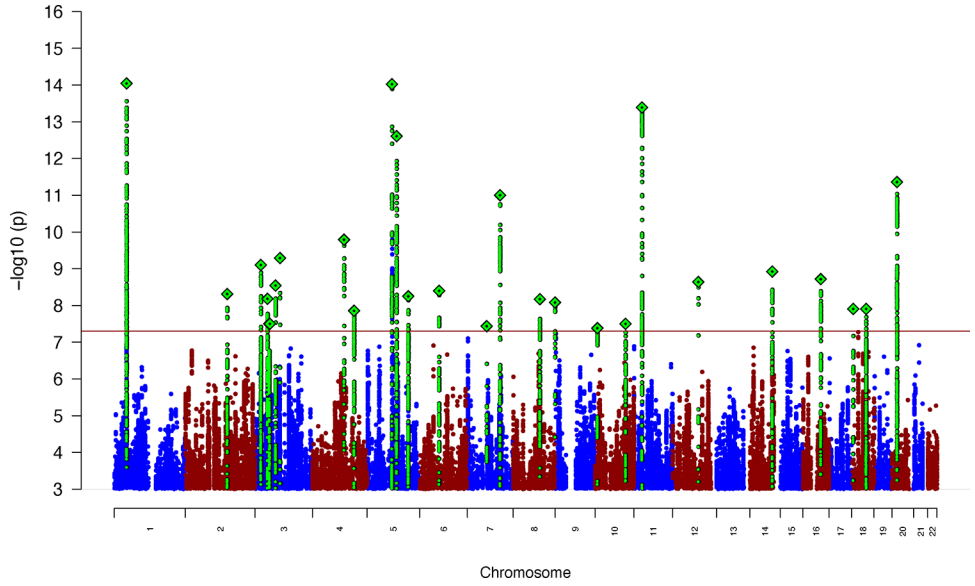

Figure 1 |. Results from GWAS meta-analysis of iPSYCH, deCODE and PGC cohorts including 38,899 cases and 186,843 controls in total.

The *y*-axis represents $-\log_{10}$(two-sided *P*-values) from meta-analysis using an inverse-variance weighted fixed effects model. Index variants in each of the genome-wide significant loci are marked as a green diamond (note that two loci on chromosome 3, index variants rs7613360 and rs2311059, are located in close proximity and therefore appear as one diamond in the plot). The red horizontal line represents the threshold for genome-wide significant association ($P = 5 \times 10^{-8}$).

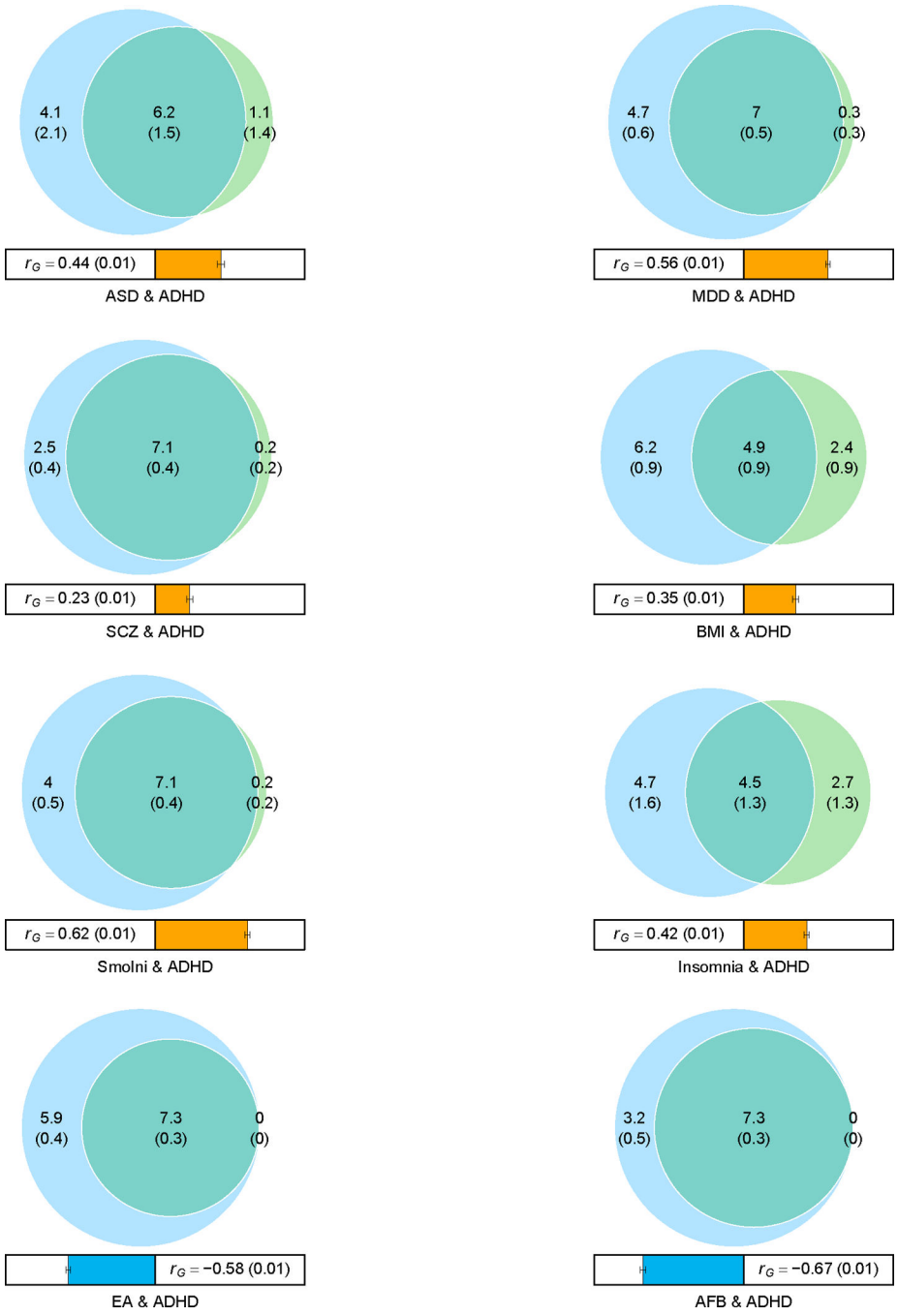

Figure 2 |. Venn diagrams showing MiXeR results of the estimated number of variants shared between ADHD and psychiatric disorders (with significant genetic correlations with ADHD) and phenotypes representing other domains with high genetic correlation with ADHD.

Circles represent shared variants (gray), unique to ADHD (light blue) and unique to the other phenotype of interest (orange). The number of shared variants (and standard deviations) is shown in thousands. The size of the circles reflects the polygenicity of each phenotype, with larger circles corresponding to greater polygenicity. The estimated genetic correlation (r_g) between ADHD and each phenotype from LDSC is shown below the corresponding Venn diagram, with an accompanying scale (−1 to +1) with blue

and red representing negative and positive genetic correlations, respectively. Bivariate results for ADHD, autism spectrum disorder (ASD), major depressive disorder (MDD), schizophrenia (SCZ), body mass index (BMI), smoking initiation (SmoIni), insomnia, educational attainment (EA) and age at first birth (AFB) are shown (see also Supplementary Table 17).

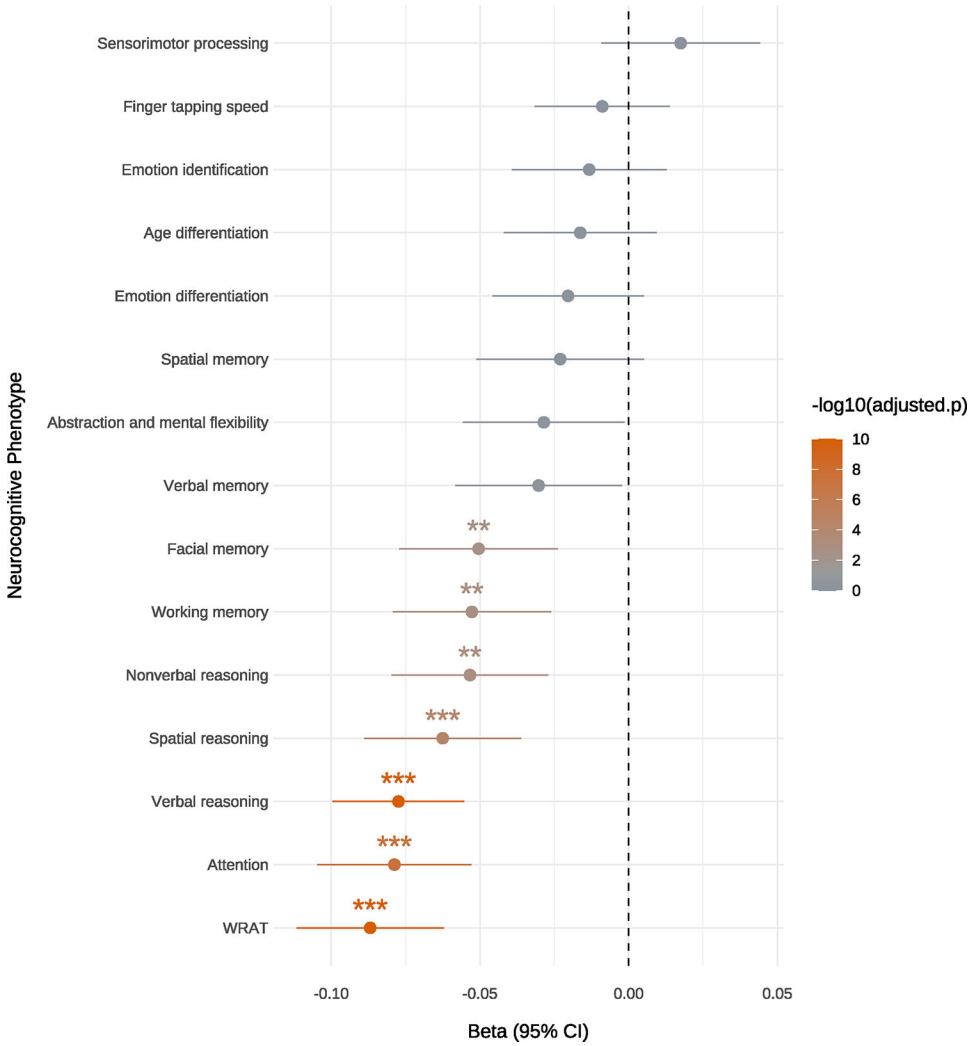

Figure 3 |. Association of ADHD-PGS with measures of cognitive abilities in the PNC cohort (*n* = 4,973).

Beta values (represented as a dot and standard errors indicated as horizontal bars) from linear regression testing for the association of ADHD-PGS with the 15 neurocognitive measures listed on the *y*-axis (Wide Range Achievement Test-4 (WRAT). The color bar at the right indicates the $-\log_{10}$(Bonferroni adjusted two-sided *P*-value) and *P*-value thresholds are indicated by stars (**P* = 0.05; ***P* = 0.01, ****P* = 0.001).

Table 1 |

Results for the 27 genome-wide significant index variants identified in the GWAS meta-analysis of 38,691 individuals with ADHD and 186,843 controls.

The location (chromosome (chr)) base position (bp) in hg19), alleles (A1 and A2), frequency (Freq.) of A1 in cases and controls, odds ratio (OR) of the effect with respect to A1, standard error (s.e.) and association *P*-values (two-sided) from inverse-variance weighted fixed effects model of the index variants are given. "Novel" indicates if the locus is a new ADHD risk locus i.e., not identified in ADHD2019 (ref. [14]). Nearby genes located within 50 kb from index variants are listed (for a list of mapped genes based on other criteria see Supplementary Table 8).

Genomic locus	chr	bp	rs ID	A1	A2	Nearby genes	Freq. cases	Freq. controls	OR	s.e.	*P*-value	Novel
1	1	44076469	rs549845	G	A	*PTPRF, KDM4A*	0.321	0.326	1.082	0.01	9.03E-15	no
2	2	145714354	rs1438898	A	C		0.762	0.769	1.065	0.01	4.88E-09	yes
3	3	20724204	rs2886697	G	A		0.634	0.643	1.061	0.01	7.90E-10	no
4	3	43691501	rs9877066	G	A	*SNRK, ANO10, ABHD5*	0.944	0.951	0.888	0.02	6.60E-09	yes
5	3	49916710	rs7613360	C	T	*TRAIP, CAMKV, MST1R, CTD-2330K9.3, MON1A*	0.598	0.614	0.948	0.01	3.18E-08	yes
6	3	51884072	rs2311059	G	A	*IQCF3, IQCF2, IQCF5, IQCF1*	0.314	0.308	0.944	0.01	3.16E-08	yes
7	3	71499401	rs17718444	C	T	*FOXP1*	0.695	0.660	1.063	0.01	2.87E-09	yes
8	3	87015142	rs114142727	C	G	*VGLL3*	0.988	0.988	1.285	0.04	5.13E-10	yes
9	4	112217523	rs17576773	C	T		0.888	0.880	1.101	0.02	1.63E-10	yes
10	4	147099654	rs6537401	G	A	*LSM6, RP11-6L6.2, SLC10A7*	0.660	0.655	0.945	0.01	1.40E-08	yes
11	5	87854395	rs4916723	A	C		0.553	0.573	0.918	0.01	9.48E-15	no
12	5	103964585	rs77960	G	A		0.665	0.682	0.929	0.01	2.46E-13	yes
13	5	144474779	rs10875612	C	T		0.483	0.470	0.947	0.01	5.62E-09	yes
14	6	70858701	rs2025286	A	C	*COL19A1*	0.553	0.550	0.947	0.01	4.00E-09	yes
15	7	67685754	rs73145587	A	T		0.910	0.901	1.107	0.02	3.67E-08	yes
16	7	114158954	rs9969232	G	A	*FOXP2*	0.344	0.382	0.934	0.01	9.98E-12	no
17	8	93277087	rs7844069	T	G		0.428	0.399	1.057	0.01	6.74E-09	yes
18	8	145802447	rs4925811	T	G	*C8orf82, ARHGAP39*	0.515	0.531	0.944	0.01	8.30E-09	yes
19	10	8784773	rs11255890	C	A		0.389	0.401	1.054	0.01	4.14E-08	yes
20	10	106453832	rs11596214	G	A	*SORCS3*	0.597	0.569	1.054	0.01	3.17E-08	no
21	11	28602173	rs2582895	C	A	*METTL15*	0.634	0.618	1.075	0.01	4.09E-14	yes
22	12	89771903	rs704061	T	C	*DUSP6, POC1B*	0.554	0.560	0.946	0.01	2.30E-09	no
23	14	98690923	rs76284431	T	A		0.847	0.842	0.922	0.01	1.19E-09	yes
24	16	61966703	rs1162202	C	T	*CDH8*	0.630	0.606	1.063	0.01	1.92E-09	yes
25	18	5871800	rs76857496	C	A	*TMEM200C*	0.870	0.859	1.083	0.01	1.24E-08	yes
26	18	50625779	rs7506904	G	A	*DCC*	0.343	0.372	0.946	0.01	1.24E-08	yes

Genomic locus	chr	bp	rs ID	A1	A2	Nearby genes	Freq. cases	Freq. controls	OR	s.e.	*P*-value	Novel
27	20	21250843	rs6082363	T	C	*XRN2, NKX2-4*	0.296	0.291	1.073	0.01	4.38E-12	yes