

Cross-disorder genetic analyses implicate dopaminergic signaling as a biological link between Attention-Deficit/Hyperactivity Disorder and obesity measures

SUPPLEMENTARY MATERIAL

Supportive information – Methods

GWAS summary statistics

The ADHD GWAS summary statistics used in our analyses are derived from iPSYCH-PGC samples, as described in details by Demontis et al. (1), and can be obtained from the PGC website (<https://www.med.unc.edu/pgc/results-and-downloads>). Data was filtered to include only SNPs with minor allele frequency (MAF) >0.01 and an imputation quality (INFO) >0.8 , totalizing 8,094,094 variants.

The BMI GWAS summary statistics were provided by the GIANT consortium and downloaded from https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. Detailed description of samples, data and analysis procedures can be found in Yengo et al. (2). After downloading, the data was subsequently filtered in order to include only SNPs with MAF >0.01 in our analyses, which yielded a total of 2,336,056 SNPs.

We also used the obesity (class I) GWAS from the GIANT consortium, which has been described in details by Berndt et al. (3). Data was downloaded from https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files and subsequently filtered to include only SNPs with MAF >0.01 , resulting in 2,353,324 SNPs.

From the ENIGMA consortium GWAS, detailed description of samples and GWAS data can be found in the original publication by Hibar et al. (4) and summary statistics are available upon request via the ENIGMA website (<http://enigma.ini.usc.edu/download-enigma-gwas-results/>). The GWASs of subcortical brain volumes were conducted adjusting for intracranial volume. The NeuroIMAGE cohort (N=154), which includes ADHD patients, was removed from the ENIGMA data prior to analyses of the current study. Only SNPs with imputation score of RSQ >0.5 are included in the ENIGMA summary statistics and we further filtered SNPs to include only those with MAF >0.01 . The final number of SNPs ranged from 8,404,06 to 8,445,488 for the different brain volumes analysed (i.e. putamen, nucleus accumbens, caudate, pallidum, amygdale, hippocampus and intracranial volume).

GWAS results from brain volumes from the UK Biobank cohort were used as replication data for any significant association found with the ENIGMA data. Detail information of these summary statistics, which include only SNPs with INFO>0.3, are provided by Elliot et al (5). Analyses were restricted to SNPs with MAF>0.01, totalizing 7,723,976 SNPs.

Candidate gene-set association analyses

Gene-set assembly

For our candidate gene-set analyses, we assembled dopaminergic neurotransmission (DOPA) and circadian rhythm (CIRCA) gene-sets based on the *Kyoto Encyclopedia of Genes and Genomes (KEGG)* and the *Gene Ontology (GO)* databases, queried in September 2016.

DOPA gene set: From the KEGG database, we included genes covered by the Dopaminergic synapse (hsa04728) and/or Tyrosine metabolism (hsa00350) pathways and from the GO database we included genes present in (at least) one of the following terms (GO: accession number): dopamine transport (GO:0015872), dopamine receptor signaling pathway (GO:0007212), dopamine receptor binding (GO:0050780), synaptic transmission, dopaminergic (GO:0001963), dopaminergic neuron axon guidance (GO:0036514), dopaminergic neuron differentiation (GO:0071542), response to dopamine (GO:1903350), and dopamine metabolic process (GO:0042417).

This resulted in 155 genes from KEGG database and 144 genes from GO, of which 24 were in common, totalizing 275 genes. From these, we found 273 genes in the MAGMA gene template ("KIF5C" and "PPP2R3B" were not present), including 9 genes located on chromosome X, which was not covered by our analyses.

CIRCA gene set: From the KEGG database, we included genes comprised by the Circadian rhythm (hsa04710) and/or Circadian entrainment (hsa04713) pathways and, from the GO database we included genes present in the circadian rhythm (GO:0007623) GO term.

This resulted in 123 genes from the KEGG database and 197 genes from GO, of which 27 were in common, totalizing 293 genes. From these, we found 290 genes in the MAGMA software gene reference template ("H0Y8X5", "LOC400927-CSNK1E", and "Q59FM5" were not present), including 6 genes located on chromosome X, which was not covered by our analyses.

Gene-set association analyses

The gene-set association analyses were performed using MAGMA software (version 1.05b; (6)). For such, SNPs were annotated to protein-coding genes, according to the location of their transcribed regions in the

Human Genome Build 37, using the NCBI 37.3 gene reference template definitions provided by MAGMA (<https://ctg.cncr.nl/software/magma>). Genes were considered as present in the GWAS summary statistics being analyzed if they contained at least one SNP located within their transcribed region. Gene-based P-values were then calculated using the SNP-wise mean model (default for summary statistics analysis), which combines the effects of SNPs within a gene and uses the sum of $-\log(\text{SNP P-value})$ as test statistic. In order to account for linkage disequilibrium (LD) between the SNPs, we used the European dataset of the 1000 Genomes Phase 3 as reference, provided at MAGMA's website (https://ctg.cncr.nl/software/MAGMA/ref_data/g1000_eur.zip).

We then performed competitive gene-set analyses, which tests whether each gene-set is differently associated with the phenotype compared to the remaining genes on the genome, while taking into account gene size, gene density and LD between genes.

Canonical pathway enrichment analysis

The sets of ADHD-BMI and ADHD-obesity overlapping genes, derived from the gene-based cross-disorder(/trait) meta-analyses, were tested for enrichment of canonical pathways using Ingenuity Pathway Analysis (<http://www.ingenuity.com>; QIAGEN Bioinformatics, Redwood City, California, USA). The Ingenuity Knowledge Base, which incorporates experimental data from published literature as well as data from many other sources, including gene expression and gene annotation databases, currently comprises 692 curated canonical pathways of functionally related and interacting genes/proteins (http://qiagen.force.com/KnowledgeBase/articles/Basic_Technical_Q_A/Available-Canonical-Pathways). For each of these pathways, Ingenuity calculates enrichment P-values using the right-tailed Fisher's exact test and taking into consideration both the total number of genes from the analyzed data set (i.e. the 211 ADHD-BMI or the 9 ADHD-obesity overlapping genes) and the total number of genes that is in the pathway in question according to the Ingenuity Knowledge Base. To account for multiple testing, the enrichment P-value of each pathway is adjusted using Benjamini-Hochberg correction, and only significantly enriched canonical pathways were reported.

Supportive information – Results

Secondary ADHD-BMI gene-based meta-analysis: no sample overlap

Since Wellcome Trust participants had been included both in the iPSYCH-PGC (1) and GIANT (2, 3) studies, we performed a secondary analysis to make sure that our results were not driven by this overlap. As described by Demontis *et al.* (1), the ADHD PGC sample from Cardiff is composed of 721 ADHD cases and 5081 Wellcome Trust controls. Therefore, we performed a secondary ADHD-BMI gene-based meta-analysis

using the leave-one-out summary statistics from the European ancestry iPSYCH-PGC ADHD GWAS without the Cardiff sample (~11% reduction in sample size). Unfortunately, it was not feasible to remove these overlapping samples from the GIANT-UK Biobank BMI GWAS. The canonical pathway enrichment findings from this secondary meta-analysis were reassuring since the *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway remained significantly associated, with seven genes in the pathway and surviving B-H correction ($P = 8.90 \times 10^{-4}$, $P_{B-H} = 4.57 \times 10^{-2}$). Since our secondary results do not show a substantial bias due to sample overlap, we opted for presenting the analysis with the largest sample size as the main analysis.

Detailed description of Figure 1

In **Figure 1**, we show a schematic representation of the *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway. In the description below, we contextualize and highlight in bold the proteins encoded by the eight genes derived from our ADHD-BMI gene-based meta-analysis results that are present in this pathway (highlighted in red in **Figure 1**).

Signaling in the *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway starts at the postsynaptic membrane where dopamine released by midbrain neurons binds and activates two types of dopamine receptors, i.e. the D1 class (DRD1 and DRD5) and D2 class (DRD2, DRD3, and DRD4) of receptors (D1 class and D2 class in **Figure 1**) (7). Subsequently, the D1 and D2 receptors work through different G protein alpha subunits to activate and inhibit the enzyme adenylylase, which results in more and less cyclic AMP (cAMP) being synthesized, respectively (7). cAMP in turn activates protein kinase A (PKA), which is inhibited by the kinase AMPK (8, 9) of which the **AMPK α** subunit is encoded by the *PRKAG1* gene (10). Activated PKA has a large number of downstream effects, including regulating the activity of L-type calcium channels (11) – of which **CACNA1D** is a subunit (10) – that are voltage-sensitive and stimulate the entry of calcium ions into neurons (12). Dopamine binding to D2 receptors also leads to a signaling cascade that results in an increased intraneuronal concentration of calcium (13). In addition, activated PKA is involved in activating transcription factors of the cAMP-dependent CREB complex (14, 15) such as **CREB3L3** (10). The CREB complex transcription factors are inhibited by the phosphatase PP1 (16) – which contains the regulatory subunit **PPP1R3A** - leading to a disruption of dopamine-induced and cAMP/PKA-dependent gene transcription, which may ultimately result in various neuropsychiatric disorders - including ADHD (17) - and somatic disorders such as obesity (18, 19). Dopamine binding and activating D1 receptors also leads to the activation of phospholipase C (PLC) enzymes (11, 20) such as **PLCL1** that binds and functionally interacts with PP1 (interaction not shown in Figure 1) (21). The above described dopamine-induced gene transcription is partially controlled by the protein 'Dopamine and cAMP Regulated Phosphoprotein-32' or DARPP-32, through a feedback loop on the cAMP/PKA cascade. Activated PKA stimulates the phosphatase PP2A - of which **PPP2R3A** is a regulatory subunit (10) - that phosphorylates DARPP-32 at Threonine(Thr)34,

which makes DARPP-32 a potent inhibitor of PP1 (16). Conversely, an increase of intracellular calcium - through being pumped into the neuron by L-type calcium channels such as **CACNA1D**, downstream of dopamine binding to D2 receptors (see above) and/or through being released from the endoplasmic reticulum (ER), a process that is mediated by the ER membrane-receptor **ITPR3 (22)** - leads to a dephosphorylation of DARPP-32 at Thr34 (23), rendering the protein inactive again. Interestingly, DARPP-32 can also be phosphorylated at Thr75 by CDK5 (16)- a kinase that itself is activated by CK1 (24), of which **CSNK1G2** is an isoform (10) - which converts DARPP-32 into an inhibitor of PKA (16). In this way, DARPP-32 is a dual-function protein that, depending on where it is phosphorylated, can act either as an inhibitor of PP1 or of PKA, which makes DARPP-32 a critical regulator of dopamine/cAMP/PKA signaling.

Supplementary Table S1. Summary of gene-based association results of the ADHD, BMI, and obesity individual GWASs, as well as of the ADHD-BMI and ADHD-obesity gene-based meta-analyses, displaying the number of genome-wide significant (GWsig) genes and if they are included in the candidate DOPA and/or CIRCA gene sets:

	GWsig genes	Presence of GWsig genes in gene sets:		
		DOPA	CIRCA	DOPA and CIRCA
ADHD ^a	20	.	.	.
BMI ^b	1747	41 (<i>ADCY5, ADCY6, AKT3, ARNTL, CACNA1C, CACNA1D, CALML6, COMT, CREB1, CREB3L1, CREB3L3, CTNNB1, DDC, DNMI1, DNMI2, DRD2, GNAI3, GNAQ, GNAS, GNB1, GNG7, GRIA1, GRIN2A, GSK3B, ITPR3, KLF16, LMX1B, OPRK1, OPRM1, PARK2, PLCB1, PLCB4, PPP1CB, PPP2R3A, PPP2R5C, PPP3CA, PTGS2, RAC1, SCN1A, SLC22A3, SLC6A4</i>)	49 (<i>ADCY3, ADCY5, ADCY6, ADCY9, ADK, AHR, ARNTL, BTBD9, BTRC, CACNA1C, CACNA1D, CALML6, CREB1, CRTCL1, DDC, DRD2, EP300, GNAI3, GNAQ, GNAS, GNB1, GNG7, GRIA1, GRIN2A, GSK3B, GUCY1A2, HCRTR1, HCRTR2, ITPR3, LGR4, NCOR1, NFIL3, NLGN1, NOS1AP, NR1H3, NTRK2, OPRL1, PLCB1, PLCB4, PPARG, PPARGC1A, PPP1CB, PRKG1, RORA, RPS6KA5, SLC6A4, SYNCRIP, TP53, ZFH3</i>)	22 (<i>ADCY5, ADCY6, ARNTL, CACNA1C, CACNA1D, CALML6, CREB1, DDC, DRD2, GNAI3, GNAQ, GNAS, GNB1, GNG7, GRIA1, GRIN2A, GSK3B, ITPR3, PLCB1, PLCB4, PPP1CB, SLC6A4</i>)
Obesity ^c	26	.	1 (<i>ADCY3</i>)	.
ADHD-BMI ^d meta-analysis	211	8 (<i>CACNA1D, CREB3L1, CREB3L3, CTNNB1, DNMI1, GRIA1, ITPR3, PPP2R3A</i>)	7 (<i>CACNA1D, GRIA1, ITPR3, PRKAG1, RPS6KA5, SYNCRIP, ZFH3</i>)	3 (<i>CACNA1D, GRIA1, ITPR3</i>)
ADHD-Obesity ^e meta-analysis	9	2 (<i>CACNA1D, DNMI1</i>)	1 (<i>CACNA1D</i>)	1 (<i>CACNA1D</i>)

^a European ancestry iPSYCH-PGC ADHD GWAS (1).

^b GIANT-UK Biobank BMI GWAS (2).

^c GIANT Obesity (class I) GWAS (3).

^{d,e} Meta-analysis of ^dADHD-BMI and ^eADHD-obesity gene-based results. Only genome-wide significant genes are shown with association P-values lower by at least one order of magnitude in the meta-analysis compared to both the ADHD and the ^dBMI or ^eobesity results individually.

Supplementary Table S2. Results of the ADHD-BMI gene-based meta-analysis showing the 211 genome-wide significant genes that increased significance in the meta-analysis by at least one order of magnitude compared to both individual GWASs.

GENE	CHR	START	STOP	ADHD gene-based results	BMI gene-based results	ADHD-BMI gene-based meta-analysis
<i>SEMA3F</i>	3	50192562	50226508	1.83X10 ⁻⁰⁴	2.27X10 ⁻²⁴	1.70X10 ⁻²⁶
<i>FBXL17</i>	5	107194734	107718080	4.08X10 ⁻⁰⁵	3.17X10 ⁻²³	2.52X10 ⁻²⁶
<i>XKR6</i>	8	10753654	11058875	1.06X10 ⁻⁰²	2.61X10 ⁻²¹	1.84X10 ⁻²²
<i>GNAT1</i>	3	50229043	50235129	1.90X10 ⁻⁰³	1.40X10 ⁻²⁰	2.14X10 ⁻²²
<i>MAML3</i>	4	140637545	141075233	4.81X10 ⁻⁰⁴	7.33X10 ⁻²⁰	4.04X10 ⁻²²
<i>CCDC171</i>	9	15552872	15971897	3.88X10 ⁻⁰³	4.14X10 ⁻²⁰	1.16X10 ⁻²¹
<i>SOX5</i>	12	23682438	24715383	9.20X10 ⁻⁰⁴	1.06X10 ⁻¹⁸	9.86X10 ⁻²¹
<i>PCDH7</i>	4	30721951	31148423	1.10X10 ⁻⁰³	7.55X10 ⁻¹⁸	8.31X10 ⁻²⁰
<i>GATA4</i>	8	11534433	11617510	7.44X10 ⁻⁰³	4.70X10 ⁻¹⁸	2.34X10 ⁻¹⁹
<i>SEMA6D</i>	15	47476403	48066420	3.11X10 ⁻¹⁰	2.34X10 ⁻¹⁴	2.42X10 ⁻¹⁹
<i>TENM2</i>	5	166406083	167691162	1.13X10 ⁻⁰²	1.36X10 ⁻¹⁷	9.78X10 ⁻¹⁹
<i>CALN1</i>	7	71244476	71912136	4.48X10 ⁻⁰⁵	3.51X10 ⁻¹⁵	6.42X10 ⁻¹⁸
<i>CACNA1D</i>	3	53529076	53847179	3.60X10 ⁻⁰⁴	6.19X10 ⁻¹⁵	3.96X10 ⁻¹⁷
<i>TRAF3</i>	14	103243816	103377837	3.15X10 ⁻⁰³	1.53X10 ⁻¹⁵	4.01X10 ⁻¹⁷
<i>NLRC3</i>	16	3589033	3627392	1.02X10 ⁻⁰²	9.63X10 ⁻¹⁶	6.38X10 ⁻¹⁷
<i>STAG1</i>	3	136055077	136471245	3.30X10 ⁻⁰³	3.02X10 ⁻¹⁵	8.34X10 ⁻¹⁷
<i>CSMD2</i>	1	33979609	34631443	9.04X10 ⁻⁰³	3.41X10 ⁻¹⁵	2.04X10 ⁻¹⁶
<i>ADARB1</i>	21	46494493	46646478	2.00X10 ⁻⁰³	1.86X10 ⁻¹⁴	3.67X10 ⁻¹⁶
<i>RSRC1</i>	3	157823690	158262624	4.44X10 ⁻⁰⁴	5.13X10 ⁻¹⁴	3.94X10 ⁻¹⁶
<i>PCCB</i>	3	135969167	136056737	2.48X10 ⁻⁰³	3.94X10 ⁻¹⁴	9.39X10 ⁻¹⁶
<i>MSL2</i>	3	135867760	135915522	2.22X10 ⁻⁰⁴	1.73X10 ⁻¹³	9.87X10 ⁻¹⁶
<i>MSI2</i>	17	55333931	55762050	1.30X10 ⁻⁰³	9.43X10 ⁻¹⁴	1.48X10 ⁻¹⁵
<i>TRAIP</i>	3	49866028	49893992	1.14X10 ⁻⁰⁴	4.02X10 ⁻¹³	1.61X10 ⁻¹⁵
<i>IP6K1</i>	3	49761728	49823973	1.54X10 ⁻⁰⁴	3.68X10 ⁻¹³	1.71X10 ⁻¹⁵
<i>CAMKMT</i>	2	44589043	44999731	1.63X10 ⁻⁰⁴	3.86X10 ⁻¹³	1.86X10 ⁻¹⁵
<i>IGF1R</i>	15	99192272	99507759	9.53X10 ⁻⁰⁴	1.46X10 ⁻¹³	1.94X10 ⁻¹⁵
<i>PPL</i>	16	4932508	4987136	8.00X10 ⁻⁰³	3.58X10 ⁻¹⁴	2.00X10 ⁻¹⁵
<i>PDE1C</i>	7	31791666	32339016	3.63X10 ⁻⁰³	7.83X10 ⁻¹⁴	2.44X10 ⁻¹⁵
<i>TEX29</i>	13	111973015	111996594	9.50X10 ⁻⁰³	4.32X10 ⁻¹⁴	2.73X10 ⁻¹⁵
<i>DNASE1</i>	16	3661772	3712689	6.14X10 ⁻⁰³	6.74X10 ⁻¹⁴	3.08X10 ⁻¹⁵
<i>ABHD17C</i>	15	80987635	81047962	9.52X10 ⁻⁰⁵	8.36X10 ⁻¹³	3.14X10 ⁻¹⁵
<i>PTBP2</i>	1	97187161	97280605	2.52X10 ⁻⁰³	1.45X10 ⁻¹³	3.62X10 ⁻¹⁵
<i>MST1</i>	3	49721380	49726196	3.96X10 ⁻⁰⁴	6.71X10 ⁻¹³	5.45X10 ⁻¹⁵
<i>BSN</i>	3	49591922	49708982	1.12X10 ⁻⁰⁵	3.85X10 ⁻¹²	5.61X10 ⁻¹⁵
<i>RNF123</i>	3	49726950	49758962	1.03X10 ⁻⁰³	4.93X10 ⁻¹³	7.21X10 ⁻¹⁵
<i>ARHGEF7</i>	13	111767624	111958081	1.87X10 ⁻⁰⁴	1.30X10 ⁻¹²	7.22X10 ⁻¹⁵
<i>PCDH9</i>	13	66876966	67804468	1.74X10 ⁻⁰³	3.79X10 ⁻¹³	7.48X10 ⁻¹⁵
<i>MEF2C</i>	5	88014058	88199922	3.27X10 ⁻⁰⁸	4.66X10 ⁻¹¹	7.80X10 ⁻¹⁵
<i>TSHZ2</i>	20	51588946	52111869	1.36X10 ⁻⁰²	1.61X10 ⁻¹³	1.37X10 ⁻¹⁴
<i>DNM1</i>	9	130965634	131017528	2.46X10 ⁻⁰⁴	2.48X10 ⁻¹²	1.76X10 ⁻¹⁴

<i>TNKS</i>	8	9412756	9639856	1.58X10-02	1.99X10-13	1.91X10-14
<i>UBN1</i>	16	4896666	4932363	4.90X10-03	4.93X10-13	1.99X10-14
<i>CLUAP1</i>	16	3550945	3589048	3.93X10-03	6.06X10-13	2.10X10-14
<i>UBA7</i>	3	49842638	49851391	9.40X10-05	5.60X10-12	2.32X10-14
<i>PURG</i>	8	30853320	30891231	3.14X10-03	8.72X10-13	2.68X10-14
<i>RPS6KA5</i>	14	91335086	91526993	6.66X10-05	7.41X10-12	2.74X10-14
<i>MON1A</i>	3	49946302	49967445	1.54X10-02	3.07X10-13	2.92X10-14
<i>ZFPM2</i>	8	106330917	106816767	2.09X10-03	1.30X10-12	3.04X10-14
<i>HIVEP2</i>	6	143072604	143267495	1.10X10-03	2.74X10-12	4.49X10-14
<i>SLC38A3</i>	3	50242692	50258406	2.18X10-04	8.20X10-12	6.19X10-14
<i>TMEM161B</i>	5	87485450	87564665	1.93X10-05	3.17X10-11	6.86X10-14
<i>RPLP2</i>	11	808841	827592	3.19X10-06	5.33X10-11	7.01X10-14
<i>TCTA</i>	3	49449639	49453909	5.22X10-04	9.34X10-12	9.80X10-14
<i>NKAIN2</i>	6	124124991	125146786	1.29X10-02	1.24X10-12	1.03X10-13
<i>LONRF2</i>	2	100889753	100939195	1.59X10-02	1.60X10-12	1.56X10-13
<i>C14orf159</i>	14	91526677	91691976	6.61X10-03	3.18X10-12	1.66X10-13
<i>DUSP6</i>	12	89741837	89746296	2.24X10-09	2.34X10-09	2.46X10-13
<i>BACE2</i>	21	42539728	42654461	1.26X10-03	1.40X10-11	2.63X10-13
<i>PPP1R3A</i>	7	113516882	113559082	1.40X10-02	4.29X10-12	3.82X10-13
<i>APEH</i>	3	49711427	49720936	7.59X10-03	6.86X10-12	3.92X10-13
<i>C3orf38</i>	3	88198875	88207115	7.37X10-03	7.05X10-12	4.02X10-13
<i>MLIP</i>	6	53883714	54131078	5.43X10-03	1.18X10-11	5.42X10-13
<i>BTBD2</i>	19	1985437	2015702	3.79X10-04	6.66X10-11	7.05X10-13
<i>ZNF131</i>	5	43120985	43176351	1.12X10-02	9.46X10-12	7.18X10-13
<i>NIM1K</i>	5	43192170	43280952	5.14X10-03	1.59X10-11	7.31X10-13
<i>GRIA1</i>	5	152870084	153193429	4.87X10-03	1.88X10-11	8.11X10-13
<i>SWI5</i>	9	131037663	131051268	1.60X10-03	3.82X10-11	8.94X10-13
<i>DIABLO</i>	12	122692209	122712081	1.45X10-02	1.01X10-11	9.36X10-13
<i>PPP2R3A</i>	3	135684515	135866752	1.04X10-02	1.46X10-11	1.07X10-12
<i>CGGBP1</i>	3	88101100	88199016	7.91X10-03	2.32X10-11	1.40X10-12
<i>TEAD3</i>	6	35441374	35464884	1.14X10-02	1.84X10-11	1.46X10-12
<i>PPARD</i>	6	35310335	35395968	1.38X10-02	1.68X10-11	1.52X10-12
<i>ATP5G1</i>	17	46970148	46973233	4.69X10-03	3.78X10-11	1.58X10-12
<i>ARHGAP1</i>	11	46698625	46722215	8.00X10-03	2.72X10-11	1.71X10-12
<i>CADPS2</i>	7	121958478	122526813	1.16X10-02	2.28X10-11	1.81X10-12
<i>TRIM38</i>	6	25962917	25987557	1.38X10-02	1.97X10-11	1.87X10-12
<i>JADE2</i>	5	133860003	133918918	9.86X10-03	2.71X10-11	1.94X10-12
<i>LOC101929490</i>	8	11537185	11555493	4.12X10-03	5.50X10-11	2.26X10-12
<i>IQSEC1</i>	3	12938542	13114652	1.12X10-03	1.25X10-10	2.47X10-12
<i>HYAL1</i>	3	50337320	50349812	7.66X10-05	4.50X10-10	3.27X10-12
<i>ZNF654</i>	3	88108394	88193814	8.17X10-03	5.48X10-11	3.46X10-12
<i>GTF2I</i>	7	74071991	74175022	7.30X10-03	6.04X10-11	3.59X10-12
<i>PIDD1</i>	11	799179	809872	5.30X10-07	4.17X10-09	4.17X10-12
<i>ULK4</i>	3	41288090	42056080	1.06X10-02	6.46X10-11	4.88X10-12
<i>HIST1H2BD</i>	6	26157419	26171577	7.23X10-03	9.75X10-11	5.98X10-12
<i>MAP4</i>	3	47892180	48130769	2.32X10-03	1.98X10-10	6.04X10-12

<i>BBX</i>	3	107241783	107530176	2.35X10-04	7.90X10-10	7.34X10-12
<i>BAK1</i>	6	33540323	33548072	3.21X10-03	2.01X10-10	7.71X10-12
<i>PNPLA2</i>	11	818901	825573	1.18X10-04	1.19X10-09	9.37X10-12
<i>ZFHX3</i>	16	72816784	73092534	5.39X10-03	2.29X10-10	1.16X10-11
<i>SLX4</i>	16	3631182	3661585	9.87X10-03	1.65X10-10	1.22X10-11
<i>DAG1</i>	3	49506136	49573051	1.61X10-03	8.15X10-10	2.09X10-11
<i>RHOA</i>	3	49396569	49449526	5.92X10-04	1.80X10-09	2.87X10-11
<i>PLCL1</i>	2	198669426	199014608	3.18X10-03	7.85X10-10	2.99X10-11
<i>TM6SF2</i>	19	19374841	19384074	1.15X10-03	1.26X10-09	3.26X10-11
<i>DHX30</i>	3	47844399	47891686	5.26X10-04	2.22X10-09	3.35X10-11
<i>SUGP1</i>	19	19387320	19431321	3.20X10-04	2.53X10-09	3.54X10-11
<i>ANTXR2</i>	4	80822771	80994626	5.62X10-05	6.63X10-09	3.82X10-11
<i>SMARCC1</i>	3	47627378	47823405	5.56X10-04	2.47X10-09	4.11X10-11
<i>KMT2D</i>	12	49412758	49453935	7.34X10-04	2.30X10-09	4.33X10-11
<i>CTNNB1</i>	3	41236401	41281939	2.24X10-04	5.32X10-09	5.75X10-11
<i>ICA1L</i>	2	203637873	203736708	2.28X10-04	5.37X10-09	6.40X10-11
<i>SCN2A</i>	2	165986659	166248820	2.87X10-03	2.00X10-09	7.44X10-11
<i>CSNK1G2</i>	19	1941148	1981337	6.30X10-05	1.13X10-08	8.74X10-11
<i>CSE1L</i>	20	47662783	47713497	9.32X10-03	1.20X10-09	8.92X10-11
<i>CSRNP3</i>	2	166326157	166545917	3.81X10-03	2.08X10-09	9.06X10-11
<i>WDPCP</i>	2	63348518	63815867	1.28X10-03	4.86X10-09	1.21X10-10
<i>ANKRD28</i>	3	15708743	15901053	2.79X10-03	3.24X10-09	1.29X10-10
<i>SLC9B2</i>	4	103946647	103998480	1.59X10-04	1.29X10-08	1.37X10-10
<i>SLC25A22</i>	11	790475	798269	6.11X10-03	2.30X10-09	1.39X10-10
<i>STK32C</i>	10	133996038	134145377	5.33X10-03	2.52X10-09	1.42X10-10
<i>ITPR3</i>	6	33587951	33664351	1.81X10-04	1.40X10-08	1.45X10-10
<i>CSPG5</i>	3	47603728	47621730	1.55X10-03	5.91X10-09	1.68X10-10
<i>IP6K3</i>	6	33689415	33714762	8.75X10-04	9.63X10-09	2.05X10-10
<i>ATP13A2</i>	1	17312453	17338467	4.97X10-03	3.97X10-09	2.12X10-10
<i>CDHR4</i>	3	49828165	49837254	1.51X10-04	2.53X10-08	2.52X10-10
<i>UQCC2</i>	6	33664538	33679528	5.88X10-04	1.50X10-08	2.67X10-10
<i>TOX3</i>	16	52471682	52581714	7.43X10-03	4.10X10-09	2.73X10-10
<i>AMBRA1</i>	11	46417962	46615619	1.03X10-03	1.14X10-08	2.80X10-10
<i>MANBA</i>	4	103552643	103682151	5.99X10-08	4.25X10-07	3.70X10-10
<i>RASGRF1</i>	15	79252289	79383215	1.15X10-03	1.48X10-08	3.79X10-10
<i>MFAP2</i>	1	17300997	17308081	7.74X10-03	5.55X10-09	3.87X10-10
<i>FOXP2</i>	7	113726365	114333827	1.10X10-06	2.01X10-07	4.03X10-10
<i>GLYR1</i>	16	4853204	4897383	8.79X10-03	5.42X10-09	4.15X10-10
<i>HIST1H4A</i>	6	26021907	26022278	7.55X10-04	2.10X10-08	5.22X10-10
<i>WDR12</i>	2	203745323	203776949	2.44X10-04	4.18X10-08	5.73X10-10
<i>BTD</i>	3	15642864	15689147	4.72X10-03	1.07X10-08	6.11X10-10
<i>GRIK5</i>	19	42502468	42574278	7.58X10-03	9.27X10-09	6.48X10-10
<i>DAGLA</i>	11	61447905	61514474	1.99X10-05	1.30X10-07	7.09X10-10
<i>LEMD2</i>	6	33738990	33756906	1.33X10-03	2.56X10-08	7.21X10-10
<i>NBEAL1</i>	2	203879597	204091101	1.15X10-03	2.51X10-08	7.56X10-10
<i>CHST10</i>	2	101008322	101034130	1.36X10-02	8.33X10-09	8.25X10-10

<i>RMDN1</i>	8	87479627	87526567	5.00X10-03	1.54X10-08	8.43X10-10
<i>CALB2</i>	16	71392616	71424341	3.91X10-03	1.99X10-08	9.69X10-10
<i>CRIM1</i>	2	36583370	36778278	7.34X10-03	1.47X10-08	1.01X10-9
<i>SLC3A1</i>	2	44502597	44547963	6.16X10-03	1.70X10-08	1.07X10-9
<i>FOXP1</i>	3	71003865	71633140	2.58X10-03	2.94X10-08	1.19X10-9
<i>HMGB4</i>	1	34326076	34330392	1.09X10-02	1.51X10-08	1.33X10-9
<i>DGKZ</i>	11	46354455	46402104	2.49X10-04	9.41X10-08	1.37X10-9
<i>ATG13</i>	11	46638826	46697569	3.07X10-03	3.09X10-08	1.39X10-9
<i>ZKSCAN4</i>	6	28212404	28227030	1.15X10-02	1.79X10-08	1.66X10-9
<i>MAD1L1</i>	7	1855428	2272583	1.58X10-03	5.93X10-08	1.93X10-9
<i>MAU2</i>	19	19431496	19469563	5.47X10-04	9.22X10-08	2.09X10-9
<i>MMP24</i>	20	33814539	33864804	1.45X10-05	4.13X10-07	2.38X10-9
<i>PREPL</i>	2	44544746	44589001	3.91X10-03	5.05X10-08	2.59X10-9
<i>DDN</i>	12	49388933	49393088	2.58X10-04	2.18X10-07	3.47X10-9
<i>UBE2D3</i>	4	103715540	103790050	4.22X10-05	4.19X10-07	3.52X10-9
<i>SLC9B1</i>	4	103806205	103947552	1.06X10-04	3.28X10-07	3.70X10-9
<i>PDDC1</i>	11	767222	777501	1.39X10-05	6.10X10-07	3.80X10-9
<i>OR4C13</i>	11	49973943	49974971	5.47X10-04	1.70X10-07	3.98X10-9
<i>BCL2L13</i>	22	18111621	18213621	4.67X10-03	7.22X10-08	4.14X10-9
<i>LOC101927844</i>	1	87678352	87717014	2.10X10-03	1.27X10-07	4.94X10-9
<i>SIDT2</i>	11	117049626	117068161	8.41X10-03	8.04X10-08	6.49X10-9
<i>GATAD2A</i>	19	19496642	19619741	4.09X10-03	1.07X10-07	6.56X10-9
<i>RPS10</i>	6	34385231	34393902	5.96X10-03	1.10X10-07	7.21X10-9
<i>NICN1</i>	3	49459766	49466777	8.41X10-05	6.79X10-07	7.21X10-9
<i>CISD2</i>	4	103749224	103813964	3.93X10-05	1.02X10-06	9.11X10-9
<i>SNX14</i>	6	86215214	86303850	8.47X10-03	1.11X10-07	9.14X10-9
<i>PHF2</i>	9	96338909	96441869	6.68X10-03	1.37X10-07	9.72X10-9
<i>GRK4</i>	4	2965232	3042474	1.41X10-03	3.46X10-07	1.19X10-8
<i>STYX</i>	14	53196883	53241707	4.02X10-03	2.18X10-07	1.23X10-8
<i>RASSF1</i>	3	50367217	50378367	1.54X10-03	3.94X10-07	1.40X10-8
<i>GRM4</i>	6	33989623	34123399	1.17X10-03	4.30X10-07	1.44X10-8
<i>HYAL3</i>	3	50330259	50336899	6.44X10-06	2.98X10-06	1.69X10-8
<i>HPS5</i>	11	18300217	18343751	3.27X10-03	3.38X10-07	1.74X10-8
<i>PMFBP1</i>	16	72152996	72206349	1.07X10-02	1.94X10-07	1.86X10-8
<i>PKP4</i>	2	159313476	159537941	8.49X10-04	6.64X10-07	1.95X10-8
<i>TMEM184B</i>	22	38612415	38669040	1.11X10-02	1.99X10-07	1.96X10-8
<i>DIS3L</i>	15	66585633	66626236	1.15X10-02	2.14X10-07	2.12X10-8
<i>FAM13A</i>	4	89647105	90032549	1.32X10-04	1.52X10-06	2.25X10-8
<i>SYNCRIP</i>	6	86317502	86353568	5.14X10-03	4.02X10-07	2.62X10-8
<i>MDH1</i>	2	63815743	63834331	2.87X10-03	5.83X10-07	2.93X10-8
<i>BANK1</i>	4	102711764	102995969	2.20X10-03	6.59X10-07	2.99X10-8
<i>SDK1</i>	7	3341080	4308632	7.22X10-03	4.50X10-07	3.60X10-8
<i>NOP14</i>	4	2939663	2965233	1.62X10-03	9.18X10-07	3.74X10-8
<i>OLFM4</i>	13	53602876	53626196	1.81X10-04	2.41X10-06	4.30X10-8
<i>KAT2B</i>	3	20081524	20195896	7.35X10-04	1.63X10-06	4.75X10-8
<i>GRID2</i>	4	93225453	94695707	2.62X10-03	1.04X10-06	5.31X10-8

<i>PEAK1</i>	15	77400498	77712446	5.80X10-03	1.11X10-06	8.30X10-8
<i>PKD1L3</i>	16	71963441	72033877	4.85X10-03	1.23X10-06	8.97X10-8
<i>CREB3L1</i>	11	46299189	46342972	4.77X10-03	1.47X10-06	1.09X10-7
<i>CREB3L3</i>	19	4153598	4173051	8.36X10-03	1.22X10-06	1.12X10-7
<i>MALRD1</i>	10	19337700	20023407	2.99X10-03	2.18X10-06	1.23X10-7
<i>THUMPD3</i>	3	9404660	9428475	5.96X10-03	1.64X10-06	1.26X10-7
<i>ADGRB2</i>	1	32192718	32230494	2.96X10-03	2.20X10-06	1.27X10-7
<i>PBXIP1</i>	1	154916553	154928624	5.91X10-03	1.74X10-06	1.40X10-7
<i>CD247</i>	1	167399877	167487847	3.08X10-04	6.06X10-06	1.43X10-7
<i>OR4C12</i>	11	50003009	50004071	5.36X10-04	5.00X10-06	1.44X10-7
<i>ZAK</i>	2	173940440	174132737	9.96X10-04	4.09X10-06	1.51X10-7
<i>PRKAG1</i>	12	49396055	49413012	8.05X10-04	4.59X10-06	1.56X10-7
<i>CELF4</i>	18	34823003	35146000	1.93X10-03	4.00X10-06	1.97X10-7
<i>TALDO1</i>	11	747417	765024	5.64X10-05	1.45X10-05	2.07X10-7
<i>MRPL21</i>	11	68658744	68671303	6.73X10-03	3.08X10-06	2.73X10-7
<i>DCC</i>	18	49866542	51062273	5.51X10-04	9.61X10-06	3.02X10-7
<i>ZNF521</i>	18	22641888	22932214	1.16X10-04	1.91X10-05	3.88X10-7
<i>CEND1</i>	11	787110	790126	2.35X10-04	1.51X10-05	3.92X10-7
<i>MARCH5</i>	10	94050920	94113721	8.80X10-04	1.02X10-05	3.93X10-7
<i>FOXO1</i>	13	41129801	41240734	4.16X10-03	6.10X10-06	4.38X10-7
<i>GALNT13</i>	2	154728426	155310489	3.93X10-03	6.45X10-06	4.50X10-7
<i>CARF</i>	2	203776978	203851060	3.37X10-04	1.73X10-05	5.51X10-7
<i>RNF115</i>	1	145610990	145689005	4.22X10-04	2.26X10-05	7.08X10-7
<i>PCSK7</i>	11	117075788	117102811	2.23X10-03	1.40X10-05	8.45X10-7
<i>ZNF564</i>	19	12636184	12691789	2.08X10-04	3.38X10-05	9.83X10-7
<i>ANO10</i>	3	43407818	43663560	4.58X10-05	7.98X10-05	1.42X10-6
<i>LIN28B</i>	6	105384874	105531207	2.87X10-03	2.20X10-05	1.50X10-6
<i>CYP20A1</i>	2	204103164	204170563	2.23X10-03	2.50X10-05	1.72X10-6
<i>ETF1</i>	5	137841782	137878989	4.74X10-03	2.38X10-05	2.01X10-6
<i>CPEB3</i>	10	93806452	94050875	6.55X10-03	2.16X10-05	2.09X10-6
<i>DPYSL5</i>	2	27070969	27173219	4.56X10-03	2.57X10-05	2.16X10-6
<i>KLHDC8B</i>	3	49208987	49213919	2.76X10-03	4.02X10-05	2.87X10-6
<i>UBE2J1</i>	6	90036344	90062619	1.88X10-03	4.71X10-05	2.94X10-6

Gene locations are given as chromosome (CHR) and transcribed region (START and STOP sites) in the Human Genome Build 37, according to the NCBI 37.3 gene definitions.

Supplementary Table S3. Results of the ADHD-obesity gene-based cross-disorder meta-analysis showing the 9 genome-wide significant genes that increased significance in the meta-analysis by at least one order of magnitude compared to both individual GWASs.

GENE	CHR	START	STOP	ADHD gene-based results	BMI gene-based results	ADHD-obesity gene-based meta-analysis
<i>BDNF</i>	11	27676440	27743605	1.13X10 ⁻⁰³	5.28X10 ⁻¹¹	1.23x10 ⁻¹²
<i>TFAP2B</i>	6	50786439	50815326	1.37X10 ⁻⁰⁴	1.20X10 ⁻⁰⁸	1.48x10 ⁻¹¹
<i>DNM1</i>	9	130965634	131017528	2.46X10 ⁻⁰⁴	2.40X10 ⁻⁰⁵	4.60x10 ⁻⁸
<i>CACNA1D</i>	3	53529076	53847179	3.60X10 ⁻⁰⁴	3.64X10 ⁻⁰⁵	9.89x10 ⁻⁸
<i>BTBD2</i>	19	1985437	2015702	3.79X10 ⁻⁰⁴	4.47X10 ⁻⁰⁵	1.22x10 ⁻⁷
<i>FBXL17</i>	5	107194734	107718080	4.08X10 ⁻⁰⁵	2.61X10 ⁻⁰⁴	1.43x10 ⁻⁷
<i>SWI5</i>	9	131037663	131051268	1.60X10 ⁻⁰³	2.00X10 ⁻⁰⁵	2.18x10 ⁻⁷
<i>CSNK1G2</i>	19	1941148	1981337	6.30X10 ⁻⁰⁵	9.00X10 ⁻⁰⁴	8.60x10 ⁻⁷
<i>CAMKMT</i>	2	44589043	44999731	1.63X10 ⁻⁰⁴	6.61X10 ⁻⁰⁴	1.17x10 ⁻⁶

Gene locations are given as chromosome (CHR) and transcribed region (START and STOP sites) in the Human Genome Build 37, according to the NCBI 37.3 gene definitions.

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