ADHD / ADD Genetic Pathway Reference

Attention-Deficit / Hyperactivity Disorder

Genetic Pathway Reference

10 functional categories • ~80 SNPs catalogued across the catecholamine, neurodevelopmental, and pharmacogenomic axes

Educational reference document | No personal genotype data | Genome build: GRCh38

1. Purpose and Scope

This document is a standalone educational reference describing the biology of attention-deficit / hyperactivity disorder (ADHD; clinically inclusive of the predominantly inattentive presentation historically called ADD), the genes that govern each node of the pathway, the well-studied common and rare variants in those genes, the cofactors and biological inputs each pathway depends on, and the supplement / pharmacological targets that map to each pathway. It is intended for use by clinicians, researchers, or interested non-specialists who want a compact pathway primer that can later be paired with personal genotype results.

All variant interpretations are based on published GWAS literature, peer-reviewed mechanistic studies, and curated variant databases (dbSNP, ClinVar, PharmGKB, CPIC). The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations. Most common variants catalogued here confer small individual effects (per-allele odds ratios 1.02–1.34); clinical significance arises from cumulative patterns and gene–environment interactions. A small number of pharmacogenomic variants — notably CYP2D6 reduced- and no-function alleles — have larger and clinically actionable effect sizes for atomoxetine therapy.

Heritability framework. Twin and family studies estimate ADHD heritability at ~74% (Faraone & Larsson, Mol Psychiatry 2019; PMID 30971954), placing it among the most heritable common psychiatric conditions. The 2023 Demontis et al. genome-wide association study meta-analysis (38,691 cases / 186,843 controls; Nat Genet 55:198–208; PMID 36702997) identified 27 genome-wide significant loci with 76 implicated genes and estimated SNP-heritability of ~14%. Most of the remaining heritability lies in additional small-effect common variants below current discovery thresholds and in rare protein-truncating variants (notably in SORCS3). ADHD shows extensive genetic correlation with major depression, autism spectrum disorder, schizophrenia, and educational attainment, with 84–98% of ADHD-influencing variants shared with at least one other psychiatric disorder.

2. Pathway Biology

2.1 What ADHD is, mechanistically

ADHD is a neurodevelopmental disorder defined by persistent inattention, impulsivity, and / or hyperactivity that begins in childhood and persists into adulthood in roughly two-thirds of cases. Worldwide prevalence is approximately 5–7% in children and 2.5–3% in adults (Faraone et al., Mol Psychiatry 2021; PMID 33627668). The clinical phenotype maps onto distributed dysfunction in three overlapping circuits: (a) the fronto-striatal loop that supports working memory, response inhibition, and reward-based decision-making; (b) the cortico-cerebellar loop that supports timing and motor sequencing; and (c) the default-mode / salience-network switch that determines whether attention is task-focused or internally drifting.

The neurochemistry of all three loops converges on catecholaminergic tone — dopamine in the striatum and ventral tegmental area, and norepinephrine in the locus coeruleus and prefrontal cortex. ADHD genetic risk is enriched in genes expressed in midbrain dopaminergic neurons and in early-developmental cortical excitatory neurons (Demontis 2023). The therapeutic targets of every approved

ADHD medication lie inside this loop: stimulants (methylphenidate, amphetamines) block DAT and NET reuptake; atomoxetine selectively blocks NET; guanfacine and clonidine are α2A-adrenergic agonists; viloxazine combines NET inhibition with serotonergic effects.

2.2 The catecholamine inverted-U

Catecholaminergic signaling has a narrow optimum: too little dopamine and norepinephrine in prefrontal cortex impairs working memory and sustained attention, but too much (as in stress, sleep deprivation, or stimulant overdose) collapses signal-to-noise via D1-receptor over-stimulation and α1 adrenergic interference. This is the inverted-U dose-response curve described by Arnsten (Nat Rev Neurosci 2009; PMID 19455173). It is the unifying biological reason why both stimulant doses and α2A agonists need to be titrated to a sweet spot, why methylphenidate non-responders sometimes do well on lower doses, and why catecholamine clearance variants (DAT1, NET, COMT) modulate not only baseline symptoms but also the position of the dose-response curve.

2.3 Catecholamine biosynthesis and cofactors

Dopamine biosynthesis begins with tyrosine, which is hydroxylated to L-DOPA by tyrosine hydroxylase (TH) — the rate-limiting step. TH absolutely requires tetrahydrobiopterin (BH4) as a redox cofactor and ferrous iron (Fe2+) as a structural cofactor; iron deficiency lowers TH activity in vivo and is one of the few modifiable peripheral biomarkers consistently associated with ADHD severity (Wang et al., Sci Rep 2017; PMID 29335617; meta-analysis SMD of serum ferritin in ADHD = −0.40, 95% CI −0.66 to −0.14). DOPA decarboxylase (DDC) then converts L-DOPA to dopamine using pyridoxal-5-phosphate (PLP, vitamin B6) as a cofactor. In noradrenergic neurons, dopamine is further hydroxylated to norepinephrine by dopamine β-hydroxylase (DBH) using copper (Cu) and ascorbate (vitamin C).

BH4 itself is synthesized by GCH1 (rate-limiting), recycled by SPR and DHFR, and oxidized to BH2 under conditions of oxidative stress; reduced BH4 supply lowers TH output and also uncouples endothelial NO synthase. The same BH4 supply is shared with serotonin synthesis (via tryptophan hydroxylase 2, TPH2) and with phenylalanine clearance (via PAH), which is why BH4 limitation has effects across all three monoaminergic systems simultaneously.

2.4 Vesicular packaging, release, and the SNARE complex

Once synthesized, monoamines are packaged into synaptic vesicles by the vesicular monoamine transporter VMAT2 (SLC18A2). Vesicle docking and fusion at the active zone is mediated by the SNARE complex — SNAP25, syntaxin-1A (STX1A), and synaptobrevin / VAMP — together with synaptotagmin-1 (SYT1) as the calcium sensor. The Coloboma mouse, which carries a deletion encompassing Snap25, displays spontaneous hyperkinetic behavior that has served as a long-standing animal model of ADHD, and SNAP25 variants in the 3'UTR (rs3746544, rs1051312) alter microRNA binding and reduce SNAP25 expression in human prefrontal cortex post-mortem (Németh et al., PLoS One 2013; PMID 23593189).

2.5 Receptors and circuit logic

Dopamine signals through five G-protein-coupled receptors: D1 and D5 (Gs-coupled, increase cAMP, broadly excitatory in striatal direct pathway) and D2, D3, D4 (Gi-coupled, decrease cAMP, broadly inhibitory in striatal indirect pathway). The DRD4 7-repeat allele (a 48-bp VNTR in exon 3) has been the most replicated dopamine-receptor finding in ADHD, with meta-analytic odds ratio approximately 1.33 (Faraone et al., Am J Psychiatry 2001; PMID 11431226; Li et al., Hum Mol Genet 2006; PMID 16774975). The DRD2 Taq1A variant (rs1800497, technically in the adjacent ANKK1 gene) tags ~30% lower striatal D2 receptor density in A1 carriers and is associated with reward-deficiency phenotypes including ADHD comorbid with substance use.

Norepinephrine signals through α1, α2, and β-adrenergic receptors. The α2A subtype (ADRA2A) is the target of guanfacine (Intuniv) and clonidine; it is densely expressed on prefrontal pyramidal cell

dendritic spines, where its activation strengthens working-memory representations. The −1291C>G promoter variant (rs1800544) modestly reduces α2A expression.

2.6 Reuptake and inactivation

Synaptic dopamine and norepinephrine are cleared primarily by the dopamine transporter DAT (SLC6A3) and the norepinephrine transporter NET (SLC6A2). Both are members of the SLC6 sodium-coupled neurotransmitter transporter family. Methylphenidate is a competitive DAT and NET blocker; amphetamines are DAT/NET substrates that reverse-transport dopamine into the cleft; atomoxetine is a selective NET inhibitor. The DAT1 3'UTR VNTR — a 40-bp repeat with 9- and 10-repeat alleles being most common — modulates DAT expression and methylphenidate response (10R/10R associated with lower MPH response in naturalistic-design meta-analyses; Frank et al., Pharmacogenomics J 2014; PMID 23588108).

Beyond reuptake, catecholamines are inactivated enzymatically by catechol-O-methyltransferase (COMT, using SAM as methyl donor and Mg2+) and by monoamine oxidases A and B (MAOA, MAOB; both FAD-dependent flavoenzymes). The COMT Val158Met polymorphism (rs4680) reduces enzyme activity by ~40% in Met/Met homozygotes — the so-called 'warrior/worrior' polymorphism — and is the most-studied catecholamine-metabolism variant in cognitive neuroscience. In prefrontal cortex, where COMT is the dominant dopamine-clearance mechanism (DAT is sparse there), Met/Met carriers have higher tonic prefrontal dopamine and tend to perform better on working-memory tasks at baseline but worse under stress.

2.7 Neurodevelopmental and synaptic-adhesion modifiers

ADHD GWAS has progressively shifted the field's attention from individual neurotransmitter-receptor genes toward early-developmental and synaptic-adhesion genes. ADGRL3 (also known as latrophilin-3, LPHN3) is an adhesion G-protein-coupled receptor that mediates excitatory presynaptic specification through interactions with teneurin and FLRT ligands. Multiple intronic ADGRL3 SNPs (rs6551665, rs1947274, rs1947275, rs2345039, rs6858066) form a haplotype associated with childhood ADHD with meta-analytic z-scores in the −2 to −3 range (Bruxel et al., Mol Psychiatry 2021; PMID 32051549). CDH13 (T-cadherin), DCC (the netrin-1 receptor), NRXN1, and PTPRF are postsynaptic-density components implicated by both common-variant GWAS (Demontis 2023) and structural-variant analyses.

FOXP1 and FOXP2 are forkhead transcription factors involved in cortical neurogenesis and cortico-striatal circuit specification. FOXP2 was originally identified through monogenic developmental verbal dyspraxia (the 'KE family'), and is now a robust GWAS hit in ADHD (rs1989903 lead variant in Demontis 2023). SORCS3 is unique in being implicated by both common-variant GWAS and rare protein-truncating variant burden — it is a sorting receptor at the postsynaptic density that regulates AMPA receptor trafficking and BDNF-TrkB signaling.

2.8 Modifiers: BDNF, iron, circadian, glutamate

BDNF (rs6265, Val66Met) reduces activity-dependent secretion of brain-derived neurotrophic factor in Met carriers and modulates long-term potentiation. Meta-analysis of fifteen ADHD case-control / TDT studies (Mei et al., Front Psychiatry 2022; PMID 35573305) found no overall association of Val66Met with ADHD risk (OR 0.95, p = 0.29), but some pharmacogenomic studies report better methylphenidate response in Val/Val homozygotes.

Iron handling intersects ADHD biology at two levels: ferritin reflects body iron stores and tracks ADHD severity (Wang 2017 meta-analysis above), and HFE / TF / TMPRSS6 variants modulate iron absorption and transport. The same iron axis is catalogued in the homocysteine, glycation, and Parkinson's disease references.

Circadian-clock variants (CLOCK rs1801260, PER2 rs2304672) are independently associated with ADHD-related sleep onset insomnia and with delayed sleep phase. ADHD shares substantial genetic correlation with insomnia traits.

Glutamatergic genes (GRIN2A, GRIN2B, GRM7) appear in multiple ADHD candidate-gene panels and in the broader Demontis 2023 effector list, reflecting the role of NMDA and metabotropic glutamate receptors in working memory and attention.

2.9 Pharmacogenomics — atomoxetine and CYP2D6

Atomoxetine is metabolized primarily by CYP2D6 to 4-hydroxyatomoxetine. CYP2D6 is highly polymorphic; reduced-function alleles (*10, *17, *41) and no-function alleles (*3, *4, *5, *6) substantially increase atomoxetine exposure. The Clinical Pharmacogenetics Implementation Consortium has issued a formal CPIC level A guideline (Brown et al., Clin Pharmacol Ther 2019; PMID 30801677): poor metabolizers may achieve clinical response at lower-than-standard doses but are also at elevated risk of adverse effects; ultrarapid metabolizers may require higher doses or therapeutic drug monitoring (target peak ~400 ng/mL). This is the only ADHD-medication gene-drug pair with a formal CPIC guideline. CYP2D6 is also relevant to viloxazine (Qelbree, partial CYP2D6 substrate) and indirectly to bupropion (CYP2D6 inhibitor).

Methylphenidate is metabolized by CES1 (carboxylesterase-1), not by cytochrome P450; the CES1 G143E variant (rs71647871) reduces hydrolysis and elevates exposure but is not yet incorporated into formal pharmacogenomic guidelines. Amphetamines are partly metabolized by CYP2D6 but the pharmacogenomic effect is smaller than for atomoxetine.

3. Functional Categories

The ADHD genetic pathway is organized into ten functional categories. Each category corresponds to a distinct biochemical or developmental job, and is the organizing scaffold for the SNP catalog in Section 4. Pharmacogenomics is treated as a tenth category by convention; for individuals with prior whole-pathway pharmacogenomic analysis, the relevant CPIC-grade findings are typically cross-referenced rather than re-derived.

#	Category	Function	Key genes
1	Catecholamine synthesis	Tyrosine → L-DOPA → dopamine → norepinephrine; cofactor supply	TH, DDC, DBH, GCH1, SPR
2	Vesicular packaging & release	VMAT2 packaging; SNARE-mediated vesicle fusion	SNAP25, STX1A, VMAT2 (SLC18A2), SYT1
3	Dopamine receptors	D1/D5 (Gs) and D2/D3/D4 (Gi) signaling	DRD1, DRD2, DRD3, DRD4, DRD5
4	Adrenergic receptors	α2A target of guanfacine; α1, β receptor signaling	ADRA2A, ADRA2C, ADRA1A
5	Reuptake transporters	DAT, NET, SERT — targets of stimulants and atomoxetine	SLC6A3 (DAT), SLC6A2 (NET), SLC6A4 (SERT)
6	Catabolism	COMT methylation (SAM/Mg) and MAO oxidation (FAD)	COMT, MAOA, MAOB
7	Serotonergic modulation	TPH2 synthesis; receptor and transporter modifiers	TPH2, HTR1B, HTR2A, HTR2C
8	Neurodevelopmental & synaptic adhesion	Excitatory synapse specification; postsynaptic density	ADGRL3, CDH13, DCC, NRXN1, PTPRF, NLGN
9	GWAS effector genes (Demontis 2023)	Common-variant signals from largest GWAS meta-analysis	FOXP1, FOXP2, SORCS3, ST3GAL3, MEF2C, PCDH7

#	Category	Function	Key genes
10	Modifiers (BDNF, iron, circadian, glutamate, PGx)	Cross-pathway modifiers and pharmacogenomic genes	BDNF, NTF3, HFE, TF, CLOCK, PER2, GRIN2A, GRM7, CYP2D6, CYP1A2, CES1

4. SNP Catalog by Functional Category

Each table below lists well-studied common and rare variants in the genes for that category, with the variant name, the functional consequence, the cofactor or biological dependency the gene's product requires, the risk allele where established, and the ClinVar or PharmGKB clinical annotation level where applicable. Effect sizes and GWAS p-values are noted in the prose around each table where well-established. The most important single reference is the Demontis et al. 2023 meta-analysis (Nat Genet 55:198–208; PMID 36702997), which identified 27 genome-wide significant ADHD risk loci with 76 implicated genes and which is referenced throughout this section as 'Demontis 2023'.

Variant tables are reference catalogs — risk-allele attribution reflects published European-ancestry effect estimates unless noted. For non-European backgrounds, allele frequencies and effect sizes may differ; this is flagged where the divergence is large.

4.1 Catecholamine synthesis

Tyrosine hydroxylase (TH) is rate-limiting for dopamine biosynthesis and depends absolutely on the BH4 cofactor (supplied by GCH1 / SPR / DHFR) and on iron. DDC depends on PLP (vitamin B6). DBH converts dopamine to norepinephrine using copper and ascorbate; the −1021C>T promoter variant (rs1611115) is functional and reduces plasma DBH activity by ~50% in T/T homozygotes (Bhaduri & Mukhopadhyay, Neurosci Lett 2008; PMID 18331769). The same BH4 / iron / B6 / Cu cofactor stack is also catalogued in the Endothelial Health, Glycation, Homocysteine, and Parkinson's disease references — supplementation strategies that support one node typically support all of them.

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
TH	rs6356	V81M	Mild effect on enzyme activity; tag for promoter VNTR	BH4, Fe2+, O2	A	Candidate, mixed
TH	rs10770141	promoter SNP	Modulates TH transcription via promoter motif	—	T	Candidate
DDC	rs921451	intron 1	Modifies DDC activity; affects L-DOPA pharmacokinetics in PD	PLP (B6)	T	Replicated PK
DBH	rs1611115	−1021C>T promoter	T allele = ~50% lower plasma DBH; reduces DA→NE conversion	Cu, vitamin C	T	Replicated functional
DBH	rs77905	intronic	Tag for DBH activity haplotype	Cu, vitamin C	—	Tag
GCH1	rs8007267	5' upstream	Modulates BH4 supply for TH and NOS3	—	A	GWAS (cross-link endothelial)
SPR	rs1876487	intronic	Sepiapterin reductase; salvages BH4	NADPH, Mg2+	—	Functional

4.2 Vesicular packaging and release

SNAP25 sits at the heart of the SNARE complex that mediates calcium-triggered vesicle fusion. The two best-studied SNAP25 variants — rs3746544 and rs1051312 — sit in the 3'UTR within microRNA-binding sites for miR-510 and miR-641, and in haplotype reduce SNAP25 expression in prefrontal cortex (Németh et al., PLoS One 2013; PMID 23593189; Liu et al., Mol Neurobiol 2017; PMID 26941099). The Coloboma mouse model (Snap25 deletion) has hyperkinetic behavior reminiscent of ADHD.

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
SNAP25	rs3746544	T1065G, 3'UTR (MnlI)	Alters miR-510/641 binding; reduces SNAP25 expression in PFC	—	T	Replicated meta-analysis
SNAP25	rs1051312	T1069C, 3'UTR (DdeI)	Alters miR binding; haplotype with rs3746544	—	C	Replicated meta-analysis
SNAP25	rs362990	intronic	A allele preferentially transmitted in ADHD trios; OR ~1.5	—	A	Replicated
SNAP25	rs362549	intronic	Component of the SNAP25 risk haplotype	—	A	Tag
SNAP25	rs362998	intronic	Three-marker haplotype with rs6108461 / rs362990	—	T	Tag
STX1A	rs941298	intronic	Tag for STX1A haplotype	—	T	Candidate
SLC18A2 (VMAT2)	rs363371	intronic	Modifies vesicular monoamine packaging	—	—	Mixed

4.3 Dopamine receptors

DRD4 has a 48-bp VNTR in exon 3 with 2- to 11-repeat alleles. The 7-repeat variant has the most-replicated common-variant association with ADHD (meta-OR ~1.33; Faraone 2001 PMID 11431226; Li 2006 PMID 16774975; Smith 2010 PMID 20468072 — stronger for ADHD combined-type). The DRD4 −521C>T promoter SNP (rs1800955) is in linkage disequilibrium with the VNTR and is the standard rsID-based proxy for DRD4 function. DRD2 Taq1A (rs1800497) sits in the adjacent ANKK1 gene; the A1 allele tags ~30% lower striatal D2 density and is associated with reward-deficiency phenotypes including ADHD-substance use comorbidity.

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
DRD4	exon 3 VNTR	7-repeat (vs 4-repeat)	Reduced cAMP response to dopamine; blunted intracellular signaling	—	7R	Meta-OR 1.33
DRD4	rs1800955	−521C>T promoter	T allele reduces transcription ~40%; LD with VNTR	—	T	Replicated proxy
DRD5	(CA)n microsatellite	148-bp allele	Tag for DRD5 promoter haplotype	—	148-bp	Meta-OR 1.34
DRD2 /	rs1800497	Taq1A; A1 allele	A1 = ~30% lower striatal D2	—	A1 (T)	Replicat

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
ANKK1			receptor density			ed
DRD2	rs2283265	intron 5	Modifies D2-short / D2-long ratio	—	T	Functional
DRD1	rs4532	−48A>G	Modifies DRD1 expression	—	G	Mixed
DRD3	rs6280	Ser9Gly	Increased D3 affinity for dopamine in Gly carriers	—	Gly (G)	Mixed

4.4 Adrenergic receptors

α2A is the target of guanfacine (Intuniv) and clonidine (Kapvay) — both FDA-approved for ADHD. The −1291C>G promoter variant (rs1800544) modestly reduces α2A expression; some pediatric studies report poorer guanfacine response in G carriers but the data are inconsistent and have not led to a CPIC guideline.

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
ADRA2A	rs1800544	−1291C>G promoter (MspI)	G allele reduces α2A expression in PFC	—	G	Replicated functional
ADRA2A	rs553668	3'UTR	Tag for α2A haplotype; modulates guanfacine response	—	A	Candidate
ADRA2C	rs13118	promoter	Affects sympathetic tone	—	—	Candidate
ADRA1A	rs1048101	Cys347Arg	Modifies α1A receptor signaling	—	—	Candidate
ADRA2A	rs521674	intronic tag	Tag for ADRA2A haplotype	—	—	Tag

4.5 Reuptake transporters

DAT (SLC6A3) is the molecular target of methylphenidate, modafinil, and the cocaine pharmacology literature. The 3'UTR VNTR (40-bp repeat, alleles 9R / 10R most common) modulates DAT expression: 10R/10R homozygotes have lower methylphenidate response in naturalistic-design meta-analysis (Frank 2014 Pharmacogenomics J, PMID 23588108). The VNTR itself is not callable from short-read WGS by simple positional lookup — rs28363170, rs6347, and rs27072 serve as tag SNPs. NET (SLC6A2) is the target of atomoxetine and viloxazine; the −3081A>T promoter SNP (rs28386840) reduces NET promoter activity by ~30% (Kim et al., PNAS 2006; PMID 16891329). SERT (SLC6A4) is included for cross-pathway relevance to depression and anxiety comorbidity.

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
SLC6A3 (DAT)	3'UTR VNTR	10-repeat (480 bp)	Modifies DAT expression; modulates MPH response	—	10R/10R = ↓MPH response	Mixed for risk; tag for PK
SLC6A3	rs28363170	tag for 3'UTR VNTR	Tag SNP, partial proxy for VNTR genotype	—	—	Tag

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
SLC6A3	rs6347	synonymous (intron)	Tag for DAT haplotype	—	A	Tag
SLC6A3	rs27072	3'UTR	LD with VNTR; tag SNP	—	T	Tag
SLC6A2 (NET)	rs28386840	−3081A>T promoter	T allele reduces NET promoter activity ~30%	—	T	Replicated functional
SLC6A2	rs5569	G1287A synonymous	Tag for NET haplotype; atomoxetine response	—	A	Replicated PD/PK
SLC6A2	rs3785143	intronic	ADHD risk + atomoxetine response (NET haplotype)	—	T	Replicated
SLC6A2	rs2242446	intronic tag	Tag for NET haplotype	—	—	Tag
SLC6A2	rs36021	intronic tag	Tag for NET haplotype	—	—	Tag
SLC6A4 (SERT)	rs25531	A>G in 5-HTTLPR	LG allele has expression similar to S allele	—	G	Modulator

4.6 Catabolism

COMT methylates catecholamines using SAM as the methyl donor and Mg2+ as the structural cofactor. The Val158Met polymorphism (rs4680) reduces enzyme activity by ~40% in Met/Met homozygotes (the 'worrier' allele); Met/Met carriers have higher tonic prefrontal dopamine, perform better on baseline working-memory tasks, and worse under stress (Mizuno et al., Sci Rep 2017; PMID 28687719). MAOA / MAOB are FAD-dependent flavoenzymes; the MAOA promoter uVNTR (3-repeat, low-activity) is associated with externalizing behavior and gene-environment effects (Caspi 2002 Science) but is not callable from rsID-based WGS query. rs6323 is the standard tag SNP for the MAOA activity haplotype.

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
COMT	rs4680	Val158Met (G→A)	Met = ~40% lower enzyme activity → higher PFC dopamine	SAM, Mg2+	Met (A) high PFC DA; Val (G) faster catabolism	Replicated cognitive modulator
COMT	rs6269	promoter (haplotype tag)	Component of pain/cognition haplotype	—	—	Replicated for haplotype
COMT	rs4818	synonymous	Codon-usage effect; component of activity haplotype	—	—	Functional
COMT	rs4633	synonymous	Component of activity haplotype	—	—	Tag
MAOA	uVNTR	3-repeat (low-activity)	Reduced MAO-A transcription; lower monoamine catabolism	FAD	3R (low)	Mixed for ADHD; G×E

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
MAOA	rs6323	T941G synonymous (X-linked)	Tag for activity haplotype	FAD	—	Tag
MAOB	rs1799836	intron 13	A allele = high activity (males)	FAD	—	Mixed
MAOA	rs2235186	intronic tag	Tag for MAOA haplotype	FAD	—	Tag

4.7 Serotonergic modulation

Tryptophan hydroxylase 2 (TPH2, the brain-specific isoform) is rate-limiting for serotonin synthesis and shares the BH4 / iron cofactor stack with TH. HTR1B is the autoreceptor controlling serotonin release; the rs6296 G allele has been the focus of multiple ADHD candidate-gene studies with meta-OR ~1.06 (Gizer et al., Hum Genet 2009; PMID 19582477).

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
TPH2	rs4570625	−703G>T promoter	T allele reduces transcription	BH4, Fe2+	T	Mixed
TPH2	rs11178997	promoter tag	Tag for TPH2 promoter haplotype	—	T	Candidate
HTR1B	rs6296	861G>C synonymous	Tag for receptor expression haplotype	—	G	Replicated meta-OR ~1.06
HTR2A	rs6313	T102C	Synonymous; tag for haplotype	—	C	Candidate
HTR2C	rs7997012	intronic	Receptor expression modifier	—	—	Candidate

4.8 Neurodevelopmental and synaptic adhesion

ADGRL3 (latrophilin-3, LPHN3) is an adhesion G-protein-coupled receptor mediating excitatory synapse specification. A four-SNP intronic haplotype (rs6551665 / rs1947274 / rs1947275 / rs2345039) confers childhood-ADHD risk in meta-analysis with z-scores in the −2 to −3 range (Bruxel et al., Mol Psychiatry 2021; PMID 32051549). Adult-ADHD signal is weaker, consistent with developmental specificity. CDH13 (T-cadherin) and DCC (netrin-1 receptor) are both Demontis 2023 GWAS hits and have been linked to cortical neurogenesis.

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
ADGRL3 (LPHN3)	rs6551665	intronic	Latrophilin-3 ADHD haplotype tag	—	A (childhood)	Replicated meta-analysis
ADGRL3	rs1947274	intronic	LPHN3 haplotype tag	—	A	Replicated
ADGRL3	rs1947275	intronic	LPHN3 haplotype tag	—	T	Replicated
ADGRL3	rs2345039	intronic	LPHN3 haplotype tag	—	C	Replicated

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
ADGRL3	rs6858066	intronic	Linked to MPH response in carriers	—	—	Candidate PK
CDH13	rs11646411	intronic	T-cadherin GWAS hit (Demontis 2019/2023)	—	C	GWAS
DCC	rs8084351	intronic	Netrin-1 receptor; Demontis 2023 GWAS hit	—	—	GWAS
PTPRF	rs2055503	intronic	Postsynaptic density component; Demontis 2023	—	—	GWAS
NLGN1	rs1572410	intronic	Neuroligin-1; postsynaptic adhesion	—	—	Candidate

4.9 GWAS effector genes (Demontis 2023)

These are common-variant genome-wide significant signals from the largest ADHD GWAS to date (Demontis et al., Nat Genet 2023; PMID 36702997). Per-allele effect sizes are small (OR ~1.02–1.10), and the loci are best interpreted in aggregate as polygenic risk. SORCS3 is unique in showing convergence between common-variant GWAS and rare protein-truncating variant burden — it is the strongest single-gene candidate for combined common+rare variant ADHD susceptibility.

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
FOXP2	rs1989903	intronic	eQTL for FOXP2 in brain; speech/language overlap	—	—	Demontis 2023 GWAS lead
FOXP2	rs12533005	intronic tag	Replicated tag in adult-ADHD brain phenotype studies	—	—	Ribasés 2012
FOXP1	rs7593947	intronic	Demontis 2023 GWAS hit	—	—	GWAS
SORCS3	rs7906286	intronic	Postsynaptic sorting; common + rare variant convergence	—	—	GWAS + rare PTV burden
ST3GAL3	rs2247493	intronic	Sialyltransferase; ADHD GWAS hit	—	—	GWAS
MEF2C	rs7714232	intronic	Synaptic transcription factor	—	—	GWAS
PCDH7	rs1556812	intronic	Protocadherin; Demontis 2019 lead	—	—	GWAS
MEF2C / PRRC2A	rs28411770	intronic	Synaptic transcription factor adjacent loci	—	—	GWAS
DUSP6	rs11420276	intronic	MAP-kinase phosphatase; Demontis 2023	—	—	GWAS

4.10 Modifiers (BDNF, iron, circadian, glutamate, pharmacogenomics)

This category contains cross-pathway modifiers (BDNF, iron handling, circadian, glutamate) and the pharmacogenomic genes most relevant to ADHD medications. The CYP2D6 entries reflect star-allele defining variants and follow CPIC level-A guidance for atomoxetine (Brown et al., Clin Pharmacol Ther 2019; PMID 30801677). Note that the full CYP2D6 phenotype call requires star-allele aggregation

across multiple defining variants and an activity score calculation, which is performed by dedicated callers (e.g., Stargazer, Aldy, PyPGx) and not by simple rsID lookup.

Gene	rsID	Variant / common name	Functional consequence	Cofactor	Risk allele	Evidence
BDNF	rs6265	Val66Met	Met allele reduces activity-dependent BDNF secretion	—	A (Met)	NS for ADHD risk; PD modifier
NTF3	rs6332	intronic	Neurotrophin-3 modifier	—	—	Candidate
HFE	rs1799945	H63D	Modifies iron handling; iron is TH cofactor	—	G	Cross-link iron axis
HFE	rs1800562	C282Y	Hemochromatosis variant; iron overload	—	A	Cross-link iron axis
TF	rs1049296	P570S	Transferrin variant; iron transport	—	T	Cross-link iron
CLOCK	rs1801260	3111T>C	C allele = evening preference, ↓ sleep efficiency	—	C	ADHD-sleep comorbidity
PER2	rs2304672	promoter	Modifies circadian phase	—	C	Cross-link sleep
GRIN2A	rs1071502	intronic	NMDA glutamate receptor subunit	—	—	Candidate
GRM7	rs6465084	intronic	mGluR7; PGC psychiatric pleiotropy	—	—	Mixed
CYP2D6	rs3892097	*4 defining (1846G>A)	No-function allele (splice); IM/PM definer	—	A (no fn)	CPIC level A — atomoxetine
CYP2D6	rs1065852	*10 defining (100C>T)	Reduced-function allele (P34S)	—	T (red fn)	CPIC level A
CYP2D6	rs5030655	*6 defining (1707delT)	No-function frameshift	—	del	CPIC level A
CYP2D6	rs28371725	*41 defining (2988G>A)	Reduced-function allele (splice)	—	A (red fn)	CPIC level A
CYP1A2	rs762551	−163C>A (*1F)	A allele = fast caffeine metabolizer (when induced)	—	A (fast)	Cross-link PD/caffeine
CYP1A2	rs2470890	intronic tag	Tag for CYP1A2 activity haplotype	—	T	Tag

5. Category → Cofactor → Supplement Target Map

This table maps each functional category to the cofactors its enzymes / signalling proteins require, the supplements that supply those cofactors or modulate the pathway pharmacologically, and the dietary /

lifestyle levers with the strongest evidence. Doses shown are general population references, not individualized recommendations. Pharmacological / Rx interventions are listed in italics.

Category	Key cofactors / nodes	Supplement / Rx targets	Diet & lifestyle levers
1. Catecholamine synthesis	BH4 (GCH1/SPR); Fe2+ (TH); PLP/B6 (DDC); Cu+vitamin C (DBH)	L-tyrosine 500–2000 mg/d; P5P 25–50 mg/d; vitamin C; iron only if deficient (ferritin); folate (BH4 recycle)	Adequate protein for tyrosine; correct ferritin <50 ng/mL
2. Vesicular packaging	Ca2+ (SYT1); ATP (vesicle loading)	Magnesium adequacy; (Rx) tetrabenazine — VMAT2 inhibitor, off-target relevance	Sleep (synaptic homeostasis)
3. Dopamine receptors	(GPCR signalling, no small-molecule cofactors)	(Rx) levodopa, dopamine agonists, antipsychotics; supplements: L-tyrosine indirect	Aerobic exercise (DA receptor sensitization)
4. Adrenergic receptors	(GPCR)	(Rx) guanfacine, clonidine, prazosin	Stress modulation; sleep
5. Reuptake transporters	Na+/Cl− gradients	(Rx) methylphenidate, amphetamine, atomoxetine, viloxazine, modafinil	Caffeine adjunct; cognitive load pacing
6. Catabolism	SAM + Mg2+ (COMT); FAD (MAO)	Magnesium 200–400 mg/d (COMT cofactor); riboflavin/FAD precursor 25–50 mg/d; (Rx) selegiline (MAO-B); SAM-e (caution: variable effect by COMT genotype)	Methyl-folate adequacy supports SAM pool
7. Serotonergic modulation	BH4, Fe2+ (TPH2); PLP (DDC)	5-HTP 50–200 mg/d (use with caution); SSRIs (Rx); inositol	Tryptophan-adequate diet; light therapy
8. Neurodevelopmental & adhesion	(no small-molecule cofactors)	Omega-3 EPA/DHA 1–3 g/d (synaptic membrane); BDNF support via aerobic exercise	Aerobic exercise; structured sleep; environmental enrichment
9. GWAS effector genes	(transcription factors, sorting receptors)	No direct supplement targets	Indirect via overall brain health
10. Modifiers	Iron (TH); FAD (MAO); BH4 (TH/TPH2)	Riboflavin 25–50 mg/d (FAD); iron only if deficient; melatonin 0.5–5 mg (circadian); (Rx) atomoxetine — CYP2D6-aware dosing per CPIC	Sleep regularity; caffeine timing; light exposure

6. Complete SNP Lookup Table

Quick reference for all SNPs catalogued in this document, sorted alphabetically by gene then by category. Coordinates are GRCh38, assembled from dbSNP build 156. The list includes principal common-variant tags, several functional candidates, and the CYP2D6 / CYP1A2 star-allele defining SNPs. Three structurally complex variants (DRD4 exon-3 VNTR, SLC6A3 3'UTR VNTR, MAOA uVNTR) cannot be enumerated by rsID and require specialized callers — they are listed by region for reference.

Gene	rsID / region	GRCh38 position	Category
TH	rs6356	11:2150126	Synthesis
TH	rs10770141	11:2161655	Synthesis

Gene	rsID / region	GRCh38 position	Category
DDC	rs921451	7:50525066	Synthesis
DBH	rs1611115	9:133636633	Synthesis
DBH	rs77905	9:136497289	Synthesis
GCH1	rs8007267	14:54870706	Synthesis (BH4)
SPR	rs1876487	2:72860010	Synthesis (BH4)
SNAP25	rs3746544	20:10218830	Release
SNAP25	rs1051312	20:10218831	Release
SNAP25	rs362990	20:10247237	Release
SNAP25	rs362549	20:10199477	Release
SNAP25	rs362998	20:10210613	Release
STX1A	rs941298	7:73505800	Release
SLC18A2 (VMAT2)	rs363371	10:118735094	Release
DRD4	exon 3 VNTR	11:637270 (region)	DA receptor
DRD4	rs1800955	11:637228	DA receptor
DRD5	(CA)n	4:9783000 (region)	DA receptor
DRD2 / ANKK1	rs1800497	11:113400106	DA receptor
DRD2	rs2283265	11:113424366	DA receptor
DRD1	rs4532	5:175420029	DA receptor
DRD3	rs6280	3:114171968	DA receptor
ADRA2A	rs1800544	10:112837802	Adrenergic
ADRA2A	rs553668	10:112839166	Adrenergic
ADRA2C	rs13118	4:3768297	Adrenergic
ADRA1A	rs1048101	8:26721337	Adrenergic
SLC6A3 (DAT)	3'UTR VNTR	5:1393466 (region)	Reuptake
SLC6A3	rs28363170	5:1393466	Reuptake (VNTR tag)
SLC6A3	rs6347	5:1394112	Reuptake
SLC6A3	rs27072	5:1392790	Reuptake
SLC6A2 (NET)	rs28386840	16:55654260	Reuptake
SLC6A2	rs5569	16:55712356	Reuptake
SLC6A2	rs3785143	16:55659277	Reuptake
SLC6A2	rs2242446	16:55708780	Reuptake
SLC6A4 (SERT)	rs25531	17:30237328	Reuptake
COMT	rs4680	22:19963747	Catabolism
COMT	rs6269	22:19951206	Catabolism
COMT	rs4818	22:19962712	Catabolism
COMT	rs4633	22:19962429	Catabolism
MAOA	uVNTR	X:43654000 (region)	Catabolism

Gene	rsID / region	GRCh38 position	Category
MAOA	rs6323	X:43654359	Catabolism
MAOA	rs2235186	X:43775067	Catabolism
MAOB	rs1799836	X:43764009	Catabolism
TPH2	rs4570625	12:71941337	Serotonergic
TPH2	rs11178997	12:71943418	Serotonergic
HTR1B	rs6296	6:78292991	Serotonergic
HTR2A	rs6313	13:46895805	Serotonergic
HTR2C	rs7997012	1:165795077	Serotonergic
ADGRL3 (LPHN3)	rs6551665	4:61530327	Neurodevelopmental
ADGRL3	rs1947274	4:61543138	Neurodevelopmental
ADGRL3	rs1947275	4:61543412	Neurodevelopmental
ADGRL3	rs2345039	4:61551722	Neurodevelopmental
ADGRL3	rs6858066	4:61555078	Neurodevelopmental
CDH13	rs11646411	16:83193007	Neurodevelopmental
DCC	rs8084351	18:52340164	Neurodevelopmental
PTPRF	rs2055503	1:44094574	Neurodevelopmental
NLGN1	rs1572410	3:62330411	Neurodevelopmental
FOXP2	rs1989903	7:114414395	GWAS effector
FOXP2	rs12533005	7:114414380	GWAS effector
FOXP1	rs7593947	3:71103538	GWAS effector
SORCS3	rs7906286	10:104619055	GWAS effector
ST3GAL3	rs2247493	1:44177812	GWAS effector
MEF2C	rs7714232	5:88187391	GWAS effector
PCDH7	rs1556812	4:30724128	GWAS effector
BDNF	rs6265	11:27658368	Modifier (BDNF)
NTF3	rs6332	12:5499798	Modifier (BDNF)
HFE	rs1799945	6:26090950	Modifier (iron)
HFE	rs1800562	6:26092912	Modifier (iron)
TF	rs1049296	3:133778705	Modifier (iron)
CLOCK	rs1801260	4:55438856	Modifier (circadian)
PER2	rs2304672	2:238822384	Modifier (circadian)
GRIN2A	rs1071502	16:9763923	Modifier (glutamate)
GRM7	rs6465084	3:7549722	Modifier (glutamate)
CYP2D6	rs3892097	22:42127941	PGx (atomoxetine)
CYP2D6	rs1065852	22:42130692	PGx (atomoxetine)
CYP2D6	rs5030655	22:42127539	PGx (atomoxetine)
CYP2D6	rs28371725	22:42129770	PGx (atomoxetine)

Gene	rsID / region	GRCh38 position	Category
CYP1A2	rs762551	15:74749575	PGx (caffeine)
CYP1A2	rs2470890	15:74756644	PGx (caffeine)

7. BCFtools Extraction Approach

Three companion files accompany this reference and live in the analysis directory:

• adhd_pathway_rsids.txt — flat list of rsIDs for VCF lookup (one per line).

• adhd_pathway_positions.bed — GRCh38 BED file as positional fallback when the VCF ID column is empty.

• adhd_pathway_extract.sh — bash wrapper that runs the rsID query, the positional fallback, computes the gap report, and (optionally) runs a BAM or CRAM spot-check on the highest-impact variants for strand and depth confirmation.

The script expects the WGS VCF in the $VCF environment variable, an optional BAM file in $BAM (no chr prefix), an optional CRAM file in $CRAM (no chr prefix) with reference fasta in $FASTA. The script emits the gap report (panel SNPs not detected, interpreted as likely homozygous reference at 60× WGS) and the spot-check tables for visual verification of the most clinically-relevant calls.

Three structural variants are NOT addressable by simple positional query: DRD4 exon-3 48-bp VNTR, SLC6A3 3'UTR 40-bp VNTR, and MAOA promoter uVNTR. The script flags these explicitly and falls back to tag SNPs (rs1800955 for DRD4; rs28363170, rs6347, rs27072 for SLC6A3; rs6323 for MAOA). Definitive VNTR genotyping requires a dedicated caller (e.g., adVNTR, GangSTR) or a long-read assay.

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