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New Insights into the Pathogenesis and Pharmacogenomics of Attention Deficit Hyperactivity Disorder

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder in which genomic, epigenomic and environmental factors are involved. ADHD is one of the most prevalent psychiatric disorders in children, affecting 8-12% of school-age children. The worldwide-pooled prevalence of mental disorders is 13.4% (anxiety disorder, 6.5%; depressive disorder, 2.6%; ADHD, 3.4%; any disruptive disorder, 5.7%) [1]. ADHD is the most frequently diagnosed neurodevelopmental disorder, with 6.4 million children and adolescents diagnosed with ADHD as of 2011 in the USA, and a current economic burden estimated in the region of $77 billion in the USA alone. 3.5 million children and adolescents are taking medication for ADHD [2]. Increasing numbers of adult ADHD patients are reported. Incidence increases exponentially; 40.4% of all patients have another psychiatric diagnosis before being diagnosed with ADHD; afterwards, 17.4% receive other diagnoses. Diagnoses contraindicating stimulants were found in 25.8% of the patients with other diagnoses before (10.5% of total) and in 40.0% (6.9% of total) after a diagnosis of ADHD. There is an increasing incidence and instability in the diagnosis of ADHD [3]. The prevalence of adult ADHD is estimated to be 3.8% in some regions. Men, when compared with women, are more likely to have ADHD (5.5% men vs. 2% women).

Biomarkers to characterize the ADHD phenotype include clinical data, psychometric assessment, laboratory analysis, brain neuroimaging, brain electrophysiology, and genomic, proteomic and metabolomic profiles [4]. These biomarkers are essential for defining the phenotypic features of the disease and for monitoring therapeutics (efficacy and safety issues) [5,6].

Phenotype

Three subtypes of the disorder have been proposed in the current clinical view of ADHD: (i) inattentive, (ii) hyperactive-impulsive, and (iii) combined type. Numerous problems are associated with ADHD: poor academic performance, learning disorders, subtle cognitive deficits, conduct disorders, antisocial personality disorder, poor social relationships, and a higher incidence of anxiety and depression symptoms into adulthood. Other clinical features include emotional instability, mental retardation, circadian rhythm disorders, epilepsy, stereotyped movements, autistic behavior, polydipsia, and an extensive plethora of potential comorbidities including oppositional defiant disorder (>60%), conduct disorder (>20%), anxiety disorder (>30%), major depression disorder (20-30%), mania/mood liability (>15%), and learning disorders (25-30%).

ADHD is associated with hypofunctional medial prefrontal cortex and orbitofrontal cortex. This network involves the lateral prefrontal cortex, the dorsal anterior cingulate cortex, the caudate nucleus and putamen. Abnormalities affecting other cortical regions and the cerebellum are also currently seen. Anatomical studies suggest widespread reductions in volume throughout the cerebrum and cerebellum, while functional imaging studies suggest that affected individuals activate more diffuse areas than controls during the performance of cognitive tasks. Reductions in volume have been observed in the total cerebral volume, the prefrontal cortex, the basal ganglia (striatum), the dorsal anterior cingulate cortex, the corpus callosum and the cerebellum. Hypoactivation of the dorsal anterior cingulate cortex, the frontal cortex and the basal ganglia have also been reported. Caudate volume is reduced in association with externalizing disorders of childhood/adolescence. Working memory deficits appear in familial high-risk offspring and those with externalizing disorders of childhood. There are specific white matter abnormalities in patients with ADHD. Different ADHD subtypes may have some overlapping microstructural damage, but they may also have unique microstructural abnormalities. ADHD-I is related to abnormalities in the temporo-occipital areas, while the combined subtype (ADHD-C) is related to abnormalities in the frontal-subcortical circuit, the fronto-limbic pathway, and the temporo-occipital areas. An abnormality in the motor circuit may represent the main difference between the ADHD-I and ADHD-C subtypes [7].

Comorbidity of ADHD with other neuropsychiatric disorders is a common phenotype worldwide. As an example, in a study of 14,825 Danish patients [8], 52.0% of the patients had at least one psychiatric disorder comorbid to ADHD and 26.2% had two or more comorbid disorders. The most frequent comorbid disorders were disorders of conduct (16.5%), specific developmental disorders of language, learning and motor development (15.4%), autism spectrum disorders (12.4%), and intellectual disability (7.9%). Male sex was generally associated with an increased risk for neuropsychiatric disorders while female sex was associated more frequently with internalizing disorders.

Genotype

ADHD is a highly heritable disorder (60-70%). Twin studies revealed that inattentive and hyperactive-impulsive ADHD symptoms were highly heritable (67% and 73%, respectively). Many candidate gene studies and genome-wide association studies (GWAS) have been conducted in search for the genetic mechanisms underlying the phenotypic expression of ADHD in different societies [9-15] (Table 1). Despite ADHD being a highly heritable disorder, most candidate genes with replicated findings across association studies only account for a small proportion of genetic variance. The genetic architecture of ADHD comprises both common and rare variants.

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Candidate genes for ADHD focused on genes involved in the dopaminergic neurotransmission system, such as DRD4, DRD5, DAT1/SLC6A3, DBH, and DDC. Genes associated with the noradrenergic (NET1/SLC6A2, ADRA2A, and ADRA2C) and serotonergic systems (5-HTT/SLC6A4, HTR1B, HTR2A, TPH2) have also received considerable interest. Additional candidate genes related to neurotransmission and neuronal plasticity that have been studied less intensively include SNAP25, CHRNA4, NMDA, BDNF, NGF, NTF3, NTF4/5, GDNF [13-15] (Table 1).

A meta-analysis for 8 common variants located in 5 top candidate genes for ADHD (BDNF, HTR1B, SLC6A2, SLC6A4 and SNAP25) revealed that a major part of the previously postulated associations were inconsistent in the pooled odds ratios. There is a weak significant association with a SNP located in the 3' UTR region of the SNAP25 gene (rs3746544, T allele). In addition to the low coverage of genetic variability given by these variants, phenotypic heterogeneity between samples (ADHD subtypes, comorbidities) and genetic background may explain these differences. Previously proposed cumulative associations with common polymorphisms in SLC6A4 and HTR1B genes were not supported [16]. However, the contribution of several candidate genes has been supported by other meta-analyses (DRD4, DRD5, DAT1, HTR1B and SNAP25), whereas others indicate that little evidence supports an important role for the 'classic' ADHD genes, with possible exceptions for SLC9A9, NOS1 and CNR1 [9]. Several genome-wide linkage studies have been conducted and, although there are considerable differences in findings between studies, several regions have been supported across several studies (bin 16.4, 5p13, 11q22-25, 17p11) [14]. Linkage studies have been successful in identifying loci for adult ADHD and led to the identification of LPHN3 and CDH13 as novel genes associated with ADHD across the lifespan [15].

Major neuropsychiatric disorders are highly heritable, with mounting evidence suggesting that these disorders share overlapping sets of molecular and cellular underpinnings. A study screening the degree of genetic commonality across six major neuropsychiatric disorders, including ADHD, anxiety disorders, autistic spectrum disorders, bipolar disorder, major depressive disorder, and schizophrenia, identified a total of 180 genes on the basis of low but liberal GWAS p-values. 22% of genes overlapped two or more disorders. The most widely shared subset of genes -common to five of six disorders - included ANK3, AS3MT, CACNA1C, CACNB2, CNNM2, CSMD1, DPCR1, ITIH3, NT5C2, PPP1R11, SYNE1, TCF4, TENM4, TRIM26, and ZNRD1. Many of the shared genes are implicated in the postsynaptic density, expressed in immune tissues and co-expressed in developing human brain. Two distinct genetic components were both shared by each of the six disorders; the 1st component is involved in CNS development, neural projections and synaptic transmission, while the 2nd is implicated in various cytoplasmic organelles and cellular processes. Combined, these genetic components account for 20-30% of the genetic load. The remaining risk is conferred by distinct, disorder-specific variants [17]. About 45 of the 85 top-ranked ADHD candidate genes encode proteins that fit into a neurodevelopmental network involved in directed neurite outgrowth. Data on copy number variations in patients with ADHD and data from animal studies provide further support for the involvement of this network in ADHD etiology [18]. What remains unknown is whether candidate genes are associated with multiple disorders via pleiotropic mechanisms, and/or if other genes are specific to susceptibility for individual disorders. Meta-analyses (1,519 meta-analyses across 157 studies) examining specific genes and specific mental disorders that have core disruptions to emotional and cognitive function and contribute most to burden of illness such as major depressive disorder, anxiety disorders (including panic disorder and obsessive compulsive disorder), schizophrenia, bipolar disorder and ADHD, identified 134 genes (206 variants) as significantly associated risk variants. Null genetic effects were also reported for 195 genes (426 variants). 13 genetic variants were shared

Symbol	Title/Gene	OMIM	Locus	Size (Kb)	Other related diseases
ADHD1	Attention deficit-hyperactivity disorder, susceptibility to, 1	608903	16p13		
ADHD2	Attention deficit-hyperactivity disorder, susceptibility to, 2	608904	17p11		
ADHD3	Attention deficit-hyperactivity disorder, susceptibility to, 3	608905	6q12		
ADHD4	Attention deficit-hyperactivity disorder, susceptibility to, 4	608906	5p13		
ADHD5	Attention deficit-hyperactivity disorder, susceptibility to, 5	612311	2q21.1		
ADHD6	Attention deficit-hyperactivity disorder, susceptibility to, 6	612312	13q12.11		
ADORA2A	Adenosine A2a receptor	102776	22q11.23	14.80 kb	
ADRA1A	Adrenergic, alpha-1A-, receptor	104221	8p21.2	117.26 kb	
ADRA2A	Adrenergic, alpha-2A-, receptor	104210	10q25.2	3.65 kb	· Susceptibility to type 2 diabetes
ADRA2C	Adrenergic, alpha-2C-, receptor	104250	4p16	1.00 kb	· Susceptibility to congestive heart failure
ADRB2	Adrenoceptor beta 2, surface	109690	5q31-q32	2.04 kb	· Susceptibility to asthma, nocturnal · Susceptibility to obesity
ANK3	Ankyrin 3, node of Ranvier (ankyrin G)	600465	10q21.2	707.23 kb	· Mental retardation, autosomal recessive, 37
APOE	Apolipoprotein E	107741	19q13.32	3.61 kb	· Alzheimer disease · Familial dysbetalipoproteinemia, hyperlipoproteinemia type III · Age related macular dystrophy, 2 · Sea-blue histiocyte disease
AS3MT	Arsenic (+3 oxidation state) methyltransferase	611806	10q24.32	32.45 kb	· Susceptibility to arsenic-dependent carcinogenesis
ASTN1	Astrotactin 1	600904	1q25.2	303.00 kb	
ASTN2	Astrotactin 2	612856	9q33.1	990.00 kb	· Susceptibility to schizophrenia
BAIAP2	BAI1-associated protein 2	605475	17q25.3	82.29 kb	

BCHE	Butyrylcholinesterase	177400	3q26.1	64.56 kb	· Apnea, postanesthetic, suxamethonium sensitivity
BDNF	Brain-derived neurotrophic factor	113505	11p14.1	67.16 kb	· WAGR complex · Central hypoventilation syndrome (congenital) · Susceptibility to anorexia nervosa and bulimia nervosa. · Susceptibility to memory impairment.
CADM2	Cell adhesion molecule 2	609938	3p12.1	342.00 kb	
CAMTA1	Calmodulin binding transcription activator 1	611501	1p36.31	984.38 kb	· Cerebellar ataxia, nonprogressive, with mental retardation
CES1	Carboxylesterase 1 (monocyte/macrophage serine esterase 1)	114835	16q12.2	30.31 kb	· Carboxylesterase 1 deficiency · Susceptibility to alteration of pharmacokinetics and drug response
CDH13	Cadherin 13, H-cadherin	601364	16q23.3	1169.62 kb	
CHRNA4	Cholinergic receptor, nicotinic, alpha polypeptide 4	118504	20q13.33	18.09 kb	· Epilepsy, nocturnal frontal lobe, type 1 · Susceptibility to nicotine addiction
CHRNA7	Cholinergic receptor, nicotinic, alpha 7 (neuronal)	118511	15q13.3	139.70 kb	· Chromosome 15q13.3 microdeletion
CLOCK	Clock circadian regulator	601851	4q12		· Susceptibility to obesity · Susceptibility to metabolic syndrome · Susceptibility to behavioral disorders
COMT	Catechol-O-methyltransferase	116790	22q11.21	28.24 kb	· Susceptibility to schizophrenia · Susceptibility to panic disorder
CYFIP1	Cytoplasmic FMR1 interacting protein 1	606322	15q11.2	110.92 kb	· Angelman syndrome
DAB2	Disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)	601236	5p13.1	53.56 kb	
DBH	Dopamine beta-hydroxylase (dopamine beta-monooxygenase)	609312	9q34	22.98 kb	· Dopamine beta-hydroxylase deficiency
DDC	Dopa decarboxylase (aromatic L-amino acid decarboxylase)	107930	7p12.1	107.02 kb	· Aromatic L-amino acid decarboxylase deficiency
DISC1	Disrupted in schizophrenia 1	605210	1q42.2	414.46 kb	· Susceptibility to schizophrenia · Susceptibility to schizoaffective disorder
DRD1	Dopamine receptor D1	126449	5q35.2	3.49 kb	
DRD2	Dopamine receptor d2	126450	11q23.2	65.68 kb	· Dystonia myoclonic
DRD4	Dopamine receptor d4	126452	11p15.5	3.40 kb	· Autonomic nervous system dysfunction · Novelty seeking personality
DRD5	Dopamine receptor d5	126453	4p16.1	2.38 kb	· Primary cervical dystonia ·Blepharospasm, primary benign
ELK3	ELK3, ETS-domain protein (SRF accessory protein 2)	600247	12q23	72.00 kb	
FADS2	Fatty acid desaturase 2	606149	11q12.2	39.00 kb	
FBXO33	F-box only protein 33	609103	14q21.1	34.00 kb	· Susceptibility to osteoporosis
FMR1	Fragile X mental retardation 1	309550	Xq27.3	39.18 kb	· Fragile X syndrome · Premature ovarian failure, fragile X-associated · Fragile-X tremor ataxia syndrome
FTO	Fat mass and obesity associated	610966	16q12.2	410.50 kb	·Growth retardation, psychomotor delay, early death · Severe obesity
GDNF	Glial cell derived neurotrophic factor	600837	5p13.2	24.03 kb	·Central hypoventilation syndrome ·Susceptibility to Hirschsprung disease
GNPDA2	Glucosamine-6-phosphate deaminase 2	613222	4p12	24.45 kb	· Susceptibility to obesity
GPRC5B	G protein-coupled receptor, family C, group 5, member B	605948	16p12.3	27.08 kb	
GPR139	G protein-coupled receptor 139		16p13.11	41.00 kb	
GRM5	Glutamate receptor, metabotropic 5	604102	11q14.3	559.07 kb	
GRM7	Glutamate receptor, metabotropic 7	604101	3p26.1-p25.1	880.29 kb	· Susceptibility to age-related hearing impairment
GUCY2C	Guanylate cyclase 2C (heat stable enterotoxin receptor)	601330	12p12.3	83.95 kb	· Diarrhea · Meconium ileus
HTR1A	5-hydroxytryptamine (serotonin) receptor 1A	109760	5q11.2-q13	1.00 kb	· Periodic fever, menstrual cycle dependent
HTR1B	5-hydroxytryptamine (serotonin) receptor 1B	182131	6q13	1.00 kb	
HTR1E	5-hydroxytryptamine (serotonin) receptor 1E	182132	6q14-q15	78.00 kb	

HTR2A	5-hydroxytryptamine (serotonin) receptor 2A	182135	13q14.2	63.48 kb	· Susceptibility to alcohol dependence · Susceptibility to anorexia nervosa · Susceptibility to obsessive-compulsive disorder · Susceptibility to schizophrenia · Susceptibility to seasonal affective disorder
HTR2C	5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled	312861	Xq24	358.68 kb	· Susceptibility to obesity · Susceptibility to behavioral disorders
ITIH3	Inter-alpha (globulin) inhibitor H3	146650	3p21.1	14.24 kb	
KALRN	Kalirin, RhoGEF kinase	604605	3q21.2	626.48 kb	· Susceptibility to coronary heart disease
KCNJ5	Potassium inwardly-rectifying channel, subfamily J, member 5	600734	11q24.3	26.65 kb	· Hyperaldosteronism, familial, type III · Long QT syndrome 13
KLF13	Kruppel-like factor 13	605328	15q13.3	51.02 kb	
LPHN3	Latrophilin 3		4q13.1	575.00 kb	
MAOA	Monoamine oxidase A	309850	Xp11.3	90.00 kb	· Brunner síndrome · MAOA/B deletion syndrome · Susceptibility to antisocial behavior
MAP2K5	Mitogen-activated protein kinase kinase 5	602520	15q23	264.43 kb	
MTHFR	Methylenetetrahydrofolate reductase (NAD(P)H)	607093	1p36.22	20.33 kb	· Homocystinuria due to MTHFR deficiency · Susceptibility to vascular disease · Susceptibility to thromboembolism · Susceptibility to schizophrenia · Susceptibility to neural tube defects
MTMR10	Myotubularin related protein 10		15q13.3	46.00 kb	
NCAM1	Neural cell adhesion molecule 1	116930	11q23.2	317.19 kb	· Susceptibility to neural tube defects · Susceptibility to alcohol dependence · Susceptibility to left ventricular wall thickness and relative wall thickness in hypertensive families
NGF	Nerve growth factor (beta polypeptide)	162030	1p13.1	52.32 kb	· Neuropathy, hereditary sensory and autonomic, type V
NGF	Nerve growth factor (beta polypeptide)	162030	1p13.1	52.32 kb	· Neuropathy, hereditary sensory and autonomic, type V
NIPA1	Non-imprinted in Prader-Willi/Angelman syndrome 1	608145	15q11.2	43.16 kb	· Spastic paraplegia 6
NIPA2	Non-imprinted in Prader-Willi/Angelman syndrome 2	608146	15q11.2	29.74 kb	Susceptibility to childhood absence epilepsy
NPSR1	Neuropeptide S receptor 1	608595	7p14.3	220.00 kb	· Susceptibility to Asthma
NTF3	Neurotrophin 3	162660	12p13.31	63.19 kb	· Severe movement defects of the limbs
NTF4	Neurotrophin 4	162662	19q13.33	3.84 kb	· Glaucoma, primary open angle, O
NTRK1	Neurotrophic tyrosine kinase, receptor, type 1	191315	1q23.1	66.10 kb	· Hereditary sensory and autonomic neuropathy, type IV
NTRK3	Neurotrophic tyrosine kinase, receptor, type 3	191316	15q25.3	379.67 kb	· Susceptibility to tumour development
NUDT3	Nudix (nucleoside diphosphate linked moiety X)-type motif 3	609228	6p21.2	104.00 kb	
PARK2	Parkinson protein 2, E3 ubiquitin protein ligase (parkin)	602544	6q26	1380.25 kb	· Parkinson disease 2, juvenile
PON1	Paraoxonase 1	168820	7q21.3	26.21 kb	· Susceptibility to coronary artery disease · Susceptibility to coronary artery spasm 2 · Microvascular complications of diabetes 5 · Sensitivity to organophosphate poisoning
PTGER4	Prostaglandin E receptor 4 (subtype EP4)	601586	5p13.1	1380.25 kb	· Susceptibility to Crohn disease
PTPRD	Protein tyrosine phosphatase, receptor type, D	601598	9p23	2298.26 kb	· Restless legs syndrome 3
SLC6A2	Solute carrier family 6 (neurotransmitter transporter), member 2	163970	16q12.2	50.56 kb	· Orthostatic intolerance
SLC6A3	Solute carrier family 6 (neurotransmitter transporter), member 3	126455	5p15.33	52.64 kb	·Parkinsonism-dystonia, infantile ·Idiopathic epilepsy · Dependence on alcohol and cocaine
SLC6A4	Solute carrier family 6 (neurotransmitter transporter), member 4	182138	17q11.2	39.58 kb	· Anxiety-related personality traits · Obsessive-compulsive disorder · Susceptibility to sudden infant death

SLC9A9	Solute carrier family 9, subfamily A (NHE9, cation proton antiporter 9), member 9	608396	3q24	583.28 kb	· Autism susceptibility 16
SNAP25	Synaptosomal-associated protein, 25kDa	600322	20p12-p11.2	88.60 kb	
STX1A	Syntaxin 1A (brain)	186590	7q11.23	20.48 kb	
SYP	Synaptophysin	313475	Xp11.23	12.40 kb	· Mental retardation, X-linked 96
SYT1	Synaptotagmin I	185605	12q21.2	588.02 kb	
TACR1	tachykinin receptor 1	162323	2p13.1	153.06 kb	
TPH2	Tryptophan hydroxylase 2	607478	12q21.1	93.00 kb	·Susceptibility to bipolar disorder · Susceptibility to major depression
TRIM32	Tripartite motif-containing 32	602290	9q33.1	26.65 kb	· Bardet-Biedl syndrome 11 · Muscular dystrophy, limb-girdle, type 2H
TSHR	Thyroid stimulating hormone receptor	603372	14q31.1	190.80 kb	· Hyperthyroidism, familial gestational · Hyperthyroidism, nonautoimmune · Hypothyroidism, congenital, nongoitrous, 1 · Thyroid adenoma, hyperfunctioning, somatic · Thyroid carcinoma with thyrotoxicosis
TUBGCP5	Tubulin, gamma complex associated protein 5	608147	15q11.2	40.49 kb	
UPF3B	UPF3 regulator of nonsense transcripts homolog B (yeast)	300298	Xq24-q26	18.00 kb	· FG syndrome 6 · Lujan-Fryns syndrome 1 ·Mental retardation, 27
VAMP2	Vesicle-associated membrane protein 2 (synaptobrevin 2)	185881	17p13.1	3.83 kb	
XKR4	XK, Kell blood group complex subunit-related family, member 4		8q12.1		

Table 1: Selected genes potentially associated with ADHD.

in common between two or more disorders (APOE e4, ACE Ins/Del, BDNF Val66Met, COMT Val158Met, DAOA G72/G30 rs3918342, DAT1 40-bp, DRD4 48-bp, SLC6A4 5-HTTLPR, HTR1A C1019G, MTHR C677T, MTHR A1298C, SLC6A4 VNTR and TPH1 218A/C) demonstrating evidence for pleiotropy [19,20].

Data from the Psychiatric Genomics Consortium [11] including 896 ADHD cases and 2,455 controls, and 2,064 parent-affected offspring trios, provided sufficient statistical power to detect gene sets representing a genotype relative risk of at least 1.17. Although all synaptic genes together showed a significant association with ADHD, this association was not stronger than that of randomly generated gene sets matched for the same number of genes. Given current sample size and gene sets based on current knowledge of genes related to synaptic function, the results reported by Hammerschlag et al. [21] do not support a major role for common genetic variants in synaptic genes in the etiology of ADHD. However, haplotypes co-segregating with ADHD-affected individuals were identified at chromosomes 1q25, 5q11-5q13, 9q31-9q32, and 18q11-18q21 in the German population [22].

Rare copy number variations (CNVs), such as chromosomal deletions or duplications, have been implicated in ADHD and other neurodevelopmental disorders. To identify rare (frequency ≤ 1%) CNVs that increase the risk of ADHD, Jarick et al. [23] performed a whole-genome CNV analysis based on 489 young ADHD patients and 1285 adult population-based controls and identified one significantly associated CNV region. In tests for a global burden of large (>500 kb) rare CNVs, they observed a nonsignificant 1.126-fold enriched rate of subjects carrying at least one such CNV in the group of ADHD cases and rare CNVs within the parkinson protein 2 gene (PARK2) with a significantly higher prevalence in ADHD patients than in controls. The PARK2 locus (chr 6: 162 659 756-162 767 019) harbored three deletions and nine duplications in the ADHD patients and two deletions and two duplications in the controls. CNVs at the PARK2 locus were found in four additional ADHD patients and one additional control. Mutations and CNVs in PARK2 are known to be associated with Parkinson's disease. 57 large, rare CNVs were identified in children with ADHD and 78 in controls, showing a significantly increased rate of CNVs in ADHD. This increased rate of CNVs was particularly high in those with intellectual disability. An excess of chromosome 16p13.11 duplications was noted in ADHD. CNVs identified in ADHD were significantly enriched for loci previously reported in both autism and schizophrenia [24].

It is commonly believed that the symptoms of ADHD are closely associated with hypo-function of the dopaminergic system. Dopamine D2 receptor activation decreases the excitability of dopamine neurons, as well as the release of dopamine. Several genes associated with the catecholaminergic system including the dopamine receptor genes (DRD4 and DRD5), the dopamine transporter gene, and the gene for dopamine beta-hydroxylase, which catalyzes conversion of dopamine to norepinephrine are associated with ADHD. ADHD is believed to be a result of abnormalities in the frontal regions of the brain, particularly the prefrontal cortex and associated subcortical structures and circuits. Underpinning these abnormalities are disturbances of catecholamine neurotransmission. Patients with ADHD have depleted levels of dopamine and norepinephrine thought to be largely the result of dysfunction of their respective transporter systems [25]. Gene and genome-wide association studies have suggested that serotoninergic gene variants are associated with increased risk of ADHD. A chronic deficit of serotonin (5-HT) at the synapse may trigger symptoms of ADHD. Serotonin through the orbitofrontal-striatal circuitry may regulate behavioral domains of hyperactivity and impulsivity interacting with abnormal dopaminergic neurotransmission in ADHD. Selective serotonin re-uptake inhibitors, L-tryptophan (the amino acid precursor of 5-HT), and non-stimulant drugs acting on the 5-HT system are modestly effective in some ADHD cases [26]. Balance between excitatory glutamate and inhibitory GABA neurotransmitter is essential and critical for proper development and functioning of brain. GABAergic (gamma aminobutyric acid) and glutamatergic

interneurons maintain excitability, integrity and synaptic plasticity. Loss of inhibitory GABA and glutamate-mediated hyper-excitation may contribute to the development of autism spectrum disorder and ADHD [27].

Proteomics and Metabolomics

Proteomics and metabolomics are still immature disciplines in ADHD. Proteomic biomarkers can be used for distinguishing between comorbid psychiatric disorders in clinical setup as well as their potential for understanding mechanisms underlying the disorders and in discovery of new treatment strategies. Metabolomics, a high-throughput investigatory strategy developed in recent years, can offer comprehensive metabolite-level insights that complement protein and genetic findings [28-30].

Treatment

The therapeutic strategies for the treatment of ADHD can be classified into 6 categories: (i) stimulants, (ii) non-stimulants, (iii) psychotropics, (iv) combination therapies, (v) multimodal interventions, and (vi) non-pharmacological treatments. Efficacious and well-tolerated medications are available for the treatment of ADHD (methylphenidate, ethylphenidate, lisdexamfetamine, atomoxetine, metadoxine, guanfacine) [31-39]. Stimulants such as methylphenidate (MPH) and amphetamines are the most widely used medications approved by the US Food and Drug Administration (FDA) for the treatment of ADHD in children. Many studies have reported the long-term efficacy and tolerability of immediate-release formulations of MPH. The disadvantages of such formulations include the need for multiple daily dosing and a potential for abuse. The efficacy and tolerability of dexmethylphenidate, the active D-isomer of MPH, in an extended-release formulation have also been reported. An extended-release formulation of mixed amphetamine salts that is dosed once daily has been found to be efficacious and well tolerated. The non-stimulant atomoxetine has been reported to be well tolerated and efficacious, although it may not be as effective as stimulants; this formulation is, however, less likely than stimulants to be associated with abuse and diversion. The pro-drug stimulant, lisdexamfetamine dimesylate, was developed to provide a long duration of effect that is consistent throughout the day, with a reduced potential for abuse. Currently available treatments for ADHD in children are efficacious and well tolerated, but many of them are limited by the requirement for multiple daily dosing, the presence of unwanted effects, and abuse potential [38].

In an US cohort, 77.8% of subjects were treated with stimulants; boys were 1.8 times more likely than girls to be treated. The median age at initiation (9.8 years), median duration of treatment (33.8 months), and likelihood of developing at least one side effect (22.3%) were not significantly different by gender. Overall, 73.1% of episodes of stimulant treatment were associated with a favorable response. The likelihood of a favorable response was comparable for boys and girls. Treatment was initiated earlier for children with either ADHD combined type or ADHD hyperactive-impulsive type than for children with ADHD predominantly inattentive type and duration of treatment was longer for ADHD combined type. There was no association between DSM-IV subtype and likelihood of a favorable response or of side effects. Dextroamphetamine and methylphenidate were equally likely to be associated with a favorable response, but dextroamphetamine was more likely to be associated with side effects [39].

Some studies indicate that parents of children with ADHD prefer to avoid stimulant medications in favor of behavioral or psychosocial interventions, while others report that parents see medication as a preferred treatment [40]. In general, only 50% of patients with ADHD receive pharmacological treatment [2].

Pharmacogenetics

There are few studies devoted to the pharmacogenetics of ADHD which might provide conclusive results with practical application in the clinical setting [41-46]; however, if compared with other brain disorders, ADHD pharmacogenetics has been relatively well documented [47].

The genes involved in the pharmacogenomic response to anti-ADHD drugs fall into five major categories: (i) genes associated with the pathogenesis of ADHD (disease-specific genes, pathogenic genes); (ii) genes associated with the mechanism of action of drugs (mechanistic genes); (iii) genes associated with drug metabolism (metabolic genes); (iv) genes associated with drug transporters; and (v) pleiotropic genes involved in multifaceted cascades and metabolic reactions (Table 2).

Methylphenidate

Pathogenic genes involved in MPH pharmacogenetics include ADRA2A, COMT, DRD2, DRD4, DRD5, SLC6A2, and SLC6A3. Mechanistic genes regulating the mechanism of action of MPH are ADRA2A, ATXN1, CES1, COMT, DRD2, DRD3, DRD4, DRD5, GRM7, NAV2, NTF3, SLC6A2, SLC6A3, and SNAP25. MPH is a substrate of CES1, and an inhibitor or CES1 and SLC6A3, and a weak inhibitor of CYP2D6. MPH is transported by SLC6A2 and SLC6A3 proteins, and probably by ABCB1 [41,47] (Table 2).

Dexmethylphenidate

Pathogenic genes affected by (or influencing) dexmethylphenidate are ADRA2A, COMT, DRD4, SLC6A2, and SLC6A3. Mechanistic genes include ADRA2A, DRD4, SLC6A2, and SLC6A3. Dexmethylphenidate is a substrate of CES1, COMT, and CYP2D6; and is transported by SLC6A2 and SLC6A3 [41,47] (Table 2).

Amphetamine

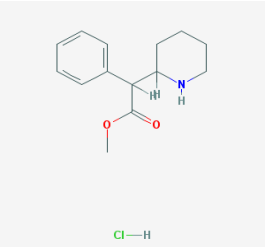
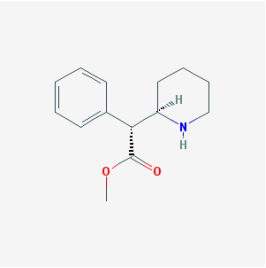
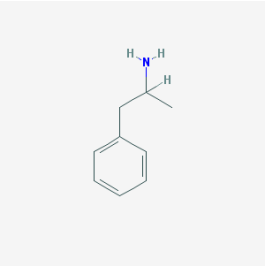
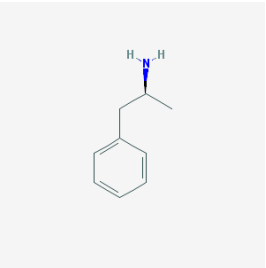
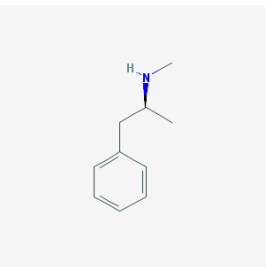
Pathogenic genes associated with amphetamine effects include ADRA2A, ADRA2C, COMT, DRD1, DRD2, DRD4, DRD5, HTR1A, HTR1D, HTR1B, MAOA, SLC6A3, SLC6A2, and SLC6A4. Mechanistic genes of amphetamine are ADRAs, ADRBs, DRDs, HTRs, MAOs, and SLC18A2. Amphetamine is a major substrate of CYP2D6 and CYP3A4, a moderate substrate of COMT, CYP2B6, and CYP19A1, a moderate inhibitor of CYP1A2, CYP2D6, and CYP3A4, and a weak inhibitor of CYP2A6. Amphetamine is transported by ABCG2, SLC6A2, SLC6A3, SLC6A4, and SLC18A2. FOS and CSNK1E are pleiotropic genes potentially involved in amphetamine effects [41,47] (Table 2).

Dextroamphetamine

Pathogenic genes associated with dextroamphetamine include CSNK1E and SLC6A3. Mechanistic genes are ADRA1A, ADRA1B, FOS, SLC6A2, SLC6A3, and SLC18A2. Dextroamphetamine is a major substrate of CYP2D6 and a minor substrate of COMT, and an inhibitor of MAOA and MAOB enzymes. Genes involved in the transport of dextroamphetamine include the protein products of the SLC6A2, SLC6A3, SLC6A4, and SLC18A2 genes [41,47] (Table 2).

Methamphetamine

Several pathogenic genes may influence the effects of

Cerebral Stimulants		
Drug	**Properties**	**Pharmacogenetics**
	**Name:** Methylphenidate Hydrochloride, Centedrine, Methylphenidate HCl, Centedrin, Concerta, Ritalin hydrochloride, Ritalin **IUPAC Name:** Methyl 2-phenyl-2-piperidin-2-ylacetate; hydrochloride **Molecular Formula:** $C_{14}H_{20}ClNO_2$ **Molecular Weight:** 269.7671 g/mol **Category:** Centrally acting sympathomimetics **Mechanism:** Blocks reuptake of norepinephrine and dopamine into presynaptic neurons. Appears to stimulate cerebral cortex and subcortical structures. **Effect:** Central Nervous System stimulant, Dopamine uptake inhibitor	**Pathogenic genes:** *ADRA2A, COMT, DRD2, DRD4, DRD5, SLC6A2, SLC6A3* **Mechanistic genes:** *ADRA2A, CES1, COMT, DRD2, DRD3, DRD4, DRD5, SLC6A2, SLC6A3, SNAP25* **Drug metabolism-related genes:** **- Substrate:** *CES1* **- Inhibitor:** *CES1, CYP2D6* (weak), *SLC6A3* **Transporter genes:** *SLC6A2, SLC6A3* **Pleiotropic genes:** *CES2*
	**Name:** Dexmethylphenidate, d-threo-Methylphenidate, D-TMP, UNII-M32RH9MFGP, CHEBI: 51860. **IUPAC Name:** Methyl (2R)-2-phenyl-2-[(2R)-piperidin-2-yl]acetate **Molecular Formula:** $C_{14}H_{19}NO_2$ **Molecular Weight:** 233.30616 g/mol **Category:** Centrally acting sympathomimetics **Mechanism:** Blocks the reuptake of norepinephrine and dopamine, and increases their release into the extraneuronal space. **Effect:** Central Nervous System stimulant, Dopamine uptake inhibitor	**Pathogenic genes:** *ADRA2A, COMT, DRD4, SLC6A2, SLC6A3* **Mechanistic genes:** *ADRA2A, DRD4, SLC6A2, SLC6A3* **Drug metabolism-related genes:** **- Substrate::** *CES1, COMT, CYP2D6* **Transporter genes:** *SLC6A2, SLC6A3* **Pleiotropic genes:** *DRD4*
	**Name:** Amphetamine, Desoxynorephedrine, 1-phenylpropan-2-amine, Mydrial, 1-Phenyl-2-aminopropane, Adderall **IUPAC Name:** 1-phenylpropan-2-amine **Molecular Formula:** $C_9H_{13}N$ **Molecular Weight:** 135.20622 g/mol **Category:** Centrally acting sympathomimetics **Mechanism:** Release of norepinephrine from stores in adrenergic nerve terminals and direct action on both α- and β- receptor sites. **Effect:** Adrenergic agent, Adrenergic uptake inhibitor, Appetite depressant, Central Nervous System stimulant, Dopamine Agent, Dopamine uptake inhibitors, MAO inhibitor	**Pathogenic genes:** *ADRA2A, ADRA2C, COMT, DRD1, DRD2, DRD4, DRD5, HTR1A, HTR1D, HTR1B, MAOA, SLC6A3, SLC6A2, SLC6A4* **Mechanistic genes:** *ADRAs, ADRBs, DRDs, HTRs, MAOs, SLC18A2* **Drug metabolism-related genes:** **-Substrate:** *COMT, CYP2B6, CYP2D6* (major), *CYP3A4* (major), *CYP19A1* **-Inhibitor:** *CYP1A2* (moderate), *CYP2A6* (weak), *CYP2D6* (moderate), *CYP3A4* (moderate), *MAO* **Transporter genes:** *ABCG2, SLC6A2, SLC6A3, SLC6A4, SLC18A2* **Pleiotropic genes:** *FOS, CSNK1E*
	**Name:** Dextroamphetamine, Dexamphetamine, D-Amphetamine, Dexamfetamine, (S)-Amphetamine, Dexedrine, (+)-Amphetamine **IUPAC Name:** (2S)-1-phenylpropan-2-amine **Molecular Formula:** $C_9H_{13}N$ **Molecular Weight:** 135.104799 g/mol **Category:** Centrally acting sympathomimetics **Mechanism:** Blocks reuptake of dopamine and norepinephrine from the synapse, thus increasing the amount of circulating dopamine and norepinephrine in the cerebral cortex to reticular activating system. Inhibits action of monoamine oxidase and causes catecholamines to be released. **Effect:** Adrenergic agent, Adrenergic uptake inhibitor, Appetite depressant, Central Nervous System stimulant, Dopamine agent, Dopamine uptake inhibitors, MAO inhibitor	**Pathogenic genes**: *CSNK1E, SLC6A3* **Mechanistic genes:** *ADRA1A, ADRA1B, FOS, SLC6A2, SLC6A3, SLC18A2* **Drug metabolism-related genes:** **-Substrate:** *COMT, CYP2D6* (major) **-Inhibitor:** *MAOA, MAOB* **Transporter genes:** *SLC6A2, SLC6A3, SLC6A4, SLC18A2*
	**Name:** Methamphetamine, Metamfetamine, d-Deoxyephedrine, d-Desoxyephedrine, d-N-Methylamphetamine, Metamphetamine, d-Phenylisopropylmethylamine **IUPAC Name:** (2S)-N-methyl-1-phenylpropan-2-amine **Molecular Formula:** $C_{10}H_{15}N$ **Molecular Weight:** 149.2328 g/mol **Category:** Centrally acting sympathomimetics **Mechanism:** Triggers a cascading release of norepinephrine, dopamine and serotonin. Acts as a dopaminergic and adrenergic reuptake inhibitor and in high concentrations as a monamine oxidase inhibitor. **Effect:** Adrenergic agent, Adrenergic uptake inhibitor, Appetite depressant, Central Nervous System stimulant, Dopamine agent, Dopamine uptake inhibitors, MAO inhibitor	**Pathogenic genes:** *ADRA2A, ADRA2C, ADRB2, ADRB3, BDNF, CNR1, COMT, CRY1, DBH, MAOA, SLC6A2, SLC6A3, SLC6A4* **Mechanistic genes:** *ADRAs, ADRBs, BDNF, CASP3, CNR1, COMT, CRY1, DBH, DTNBP1, MAOA, MAOB, GAD2, GABRs, GSTM1, GSTP1, SLC6A2, OPRM1, SLC6A3, SLC6A4, SLC6A9, SLC18A2, SLC22A3, TAAR1* **Drug metabolism-related genes:** **-Substrate:** *CYP1A2, CYP2D6* (major), *CYP2E1, CYP3A4* **-Inhibitor:** *BCL2, BAX, COX, CRY1, GSTA3, GSTM1, MAOA, TH* **Transporter genes:** *SLC6A2, SLC6A3, SLC6A4, SLC6A9, SLC18A2, SLC22A3, SLC22A5* **Pleiotropic genes:** *PARK2*

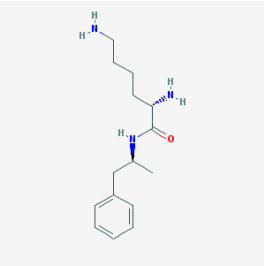
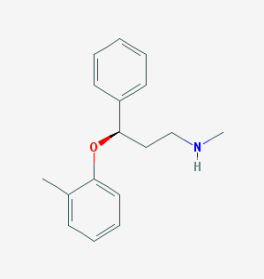
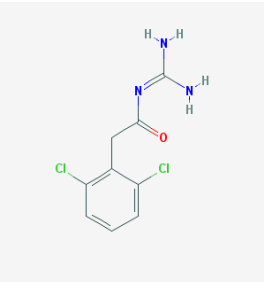
	**Name:** Lisdexamfetamine, UNII-H645GUL8KJ, NRP104, 608137-32-2, DB01255, LS-187377 **IUPAC Name:** (2S)-2,6-diamino-N-[(2S)-1-phenylpropan-2-yl] hexanamide **Molecular Formula:** $C_{15}H_{25}N_3O$ **Molecular Weight:** 263.3785 g/mol **Category:** Centrally acting sympathomimetics **Mechanism:** Blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. **Effect:** Central Nervous System Stimulant	**Pathogenic genes:** *COMT, MAOA, SLC6A2, SLC6A3, SLC6A4* **Mechanistic genes:** *CSNK1E, SLC6A2, SLC6A3* **Drug metabolism-related genes:** **-Substrate:** *CYP2D6* **-Inhibitor:** *MAOA, MAOB7* **Transporter genes:** *SLC6A2, SLC6A3, SLC6A4* **Pleiotropic genes:** *CYP3A4*
NON-STIMULANTS AGENTS		
Drug	**Properties**	**Pharmacogenetics**
	**Name:** Atomoxetine Hydrochloride, Tomoxetine, Tomoxetina, Tomoxetinum, (-)-Tomoxetine, Strattera, Tomoxetinum. **IUPAC Name:** (3R)-N-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine **Molecular Formula:** $C_{17}H_{21}NO$ **Molecular Weight:** 255.35474 g/mol **Category:** Norepinephrine Reuptake Inhibitor. **Mechanism:** Selectively inhibits the presynaptic norepinephrine transporter. **Effect:** Adrenergic uptake inhibitor, Antidepressive agent	**Pathogenic genes:** *ADRA2C, DRD4, SLC6A2, SLC6A3* **Mechanistic genes:** *SLC6A2* **Drug metabolism-related genes:** **-Substrate:** *CYP2C19* (minor), *CYP2D6* (major) **-Inhibitor:** *CES1, CYP1A2* (weak), *CYP2C9* (weak), *CYP2D6* (moderate), *CYP3A4* (moderate), *SLC6A2* **Transporter genes:** *SLC6A2, SLC6A3* **Pleiotropic genes:** *DRD4*
	**Name:** Guanfacine**,** Intuniv, Estulic, Guanfacinum, Guanfacina. **IUPAC Name:** N-carbamimidoyl-2-(2,6-dichlorophenyl)acetamide **Molecular Formula:** $C_9H_9Cl_2N_3O$ **Molecular Weight:** 246.09326 g/mol **Category:** Adrenergic alpha-2 Receptor Agonists **Mechanism**: Selectively stimulates central alpha(2)-adrenergic receptors, resulting in inhibition of sympathetic vasomotor centers. **Effect:** Antihypertensive effects, Adrenergic alpha-agonists, Strengthening prefrontal cortex functions	**Pathogenic genes:** *ADRA1B , ADRA2A* **Mechanistic genes:** *ADRA2A* **Drug metabolism-related genes:** **-Substrate:** *ABCB1, CYP3A4* **Transporter genes:** *ABCB1*

Table 2: Pharmacological profile and pharmacogenetics of agents for the treatment of ADHD.

methamphetamine, including ADRA2A, ADRA2C, ADRB2, ADRB3, BDNF, CNR1, COMT, CRY1, DBH, MAOA, SLC6A2, SLC6A3, and SLC6A4. Abundant mechanistic genes participate in its mechanism of action at different levels (ADRAs, ADRBs, BDNF, CASP3, CNR1, COMT, CRY1, DBH, DTNBP1, MAOA, MAOB, GAD2, GABRs, GSTM1, GSTP1, SLC6A2, OPRM1, SLC6A3, SLC6A4, SLC6A9, SLC18A2, SLC22A3, and TAAR1). Methamphetamine is a major substrate of CYP2D6, a minor substrate of CYP1A2, CYP2E1, and CYP3A4, and an inhibitor of BCL2, BAX, COX, CRY1, GSTA3, GSTM1, MAOA, and TH. Methamphetamine is transported by SLC6A2, SLC6A3, SLC6A4, SLC6A9, SLC18A2, SLC22A3, and SLC22A5 gene products. The PARK2 gene is also involved in methamphetamine efficacy and safety issues [41,47] (Table 2).

Lisdexamfetamine

Lisdexamfetamine is a mayor substrate of CYP2D6 and CYP3A4, and inhibitor of MAOA and MAOB7. Pathogenic genes involved in lisdexamfetamine effects are COMT, MAOA, SLC6A2, SLC6A3, and SLC6A4. CSNK1E, SLC6A2, and SLC6A3 may act as mechanistic genes. SLC6A2, SLC6A3, and SLC6A4 are major transporters of lisdexamfetamine [41,47] (Table 2).

Atomoxetine

Atomoxetine is a major substrate of CYP2D6, a minor substrate of CYP2C19, a moderate inhibitor of CYP2D6 and CYP3A4, and a weak inhibitor of CES1, CYP1A2, CYP2C9, CYP2D6, and SLC6A2. The pathogenic genes involved in the effects of atomoxetine are ADRA2C, DRD4, SLC6A2, and SLC6A3; and it's most important mechanistic gene is SLC6A2. SLC6A2 and SLC6A3 participate in the transport of atomoxetine [41,47] (Table 2).

Guanfacine

Guanfacine is a substrate of ABCB1 and CYP3A4. ADRA1B and ADRA2A are pathogenic genes involved in guanfacine effects, and ADRA2A is the most important mechanistic gene. ABCB1 is a fundamental transporter for guanfacine intro the BBB [41,47] (Table 2).

Conclusions

Although pharmacological and alternative treatments have been used in children with ADHD to ameliorate their behavioral symptomatology, at the present time pharmacological treatment with stimulants, non-stimulant medications and psychotropic drugs appears to be the most effective form of therapeutic intervention, not devoid of side-effects. Recent advances in drug development and pharmacogenomics predict a better future in terms of novel therapeutic options in order to avoid the still unknown long-term consequences derived from the chronic administration of conventional

drugs on brain, cardiovascular, metabolic and endocrine functions. It is important to assume that by trial-and-error, without information on the pharmacogenetic profiles of ADHD patients, only 30% of the children receive the appropriate medication at the right dosage [47]. In this regard, the introduction of pharmacogenetic procedures in clinical practice is the best option for the optimization of therapeutics while reducing costs and adverse drug reactions.

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