Genomic Profiling of ADHD

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Abstract

The inheritance of attention-deficit hyperactivity disorder (ADHD) is more common in children and adults and therefore more research in the field of genetics was carried out. The experiments indicated that the genetic factors played a crucial role in the etiology and course of the disease. Numerous studies initially focused on the candidate genes for ADHD particularly those genes involved in the dopaminergic, noradrenergic, and serotonergic neurotransmission systems. In the recent past, the association of ADHD with the candidate genes linked to neuronal growth and plasticity, and the glutaminergic system, has been published. This chapter reviews the single-nucleotide polymorphisms found in the candidate genes and recaps the results of genome-wide association studies (GWAS). GWAS helps in the discovery of new ADHD genes in a hypothesis-free manner. The GWAS findings are redirecting the future of the ADHD research towards novel gene systems and processes. The association between genetic experts (researchers), clinicians, and statisticians is needed in the future to identify more novel ADHD genes.

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6.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disease that affects up to 8–12% of children globally. About 65% of them have ADHD symptoms and neuropsychological problems even in adulthood. ADHD symptoms reversely affect various aspects in the child's or adult's academic success, health, and social relationship with their families, friends, and society. Academic and communal outputs, stressed child-parent associations, and enhanced consumption and expenses on healthcare services are notable outcomes. In the early years of the twentieth century, people believed that children with hyperactive symptoms suffered from a gloomy fault of decent control. During the period of 1930s, theories indicating the involvement of slight brain damage and/or brain dysfunction originated based on the resemblance of behavioral disturbances seen in encephalitis or traumatic birth. The therapeutic role of amphetamines for the management of ADHD symptoms was also demonstrated at the same time. Initially, the disease was termed as the "hyperactive child syndrome" and renamed to "hyperactive reaction of childhood." In the 1980s, the term "attention-deficit disorder" was introduced by DSM-III, and finally in 1994 it was coined as "attention-deficit hyperactivity disorder" in DSM-IV (Polanczyk et al. 2015). The causes of ADHD are proved to be more complex.

Some reports indicated that there are differences in the ADHD inheritance of children (75–90%) and adults (30–50%) (Faraone and Mick 2010) whereas other studies found higher prevalence in adults (Faraone et al. 2000). The candidate gene, linkage, and genome-wide association studies (GWAS) demonstrated that the occurrence of 40% of ADHD inheritance was accounted by the polygenic responsibility containing single-nucleotide polymorphisms (SNPs) (more common variants) and copy number variants (insertions/deletions) (Lee et al. 2013; Martin et al. 2015). The GWAS (Demontis et al. 2017; Grove et al. 2019; Pardiñas et al. 2018) carried out in the children with ADHD, schizophrenia, and autism found 12, 145, and 5 autonomous linked loci, respectively. Although most cases of ADHD occur due to genetic disturbances, the exposure to environmental toxins and their interactions also contribute to the risk of ADHD (Banerjee et al. 2007). Previous studies indicated that the risk of ADHD increased due to exposure to environmental contaminants like polychlorinated biphenyls and lead (Eubig et al. 2010), and biological factors including very low birth weight of babies (Hack et al. 2009), prenatal exposure to nicotine (Ernst et al. 2001), stress (Rodriguez and Bohlin 2005) and alcohol (Han et al. 2015).

6.2 Genetic Overlap

Various twin and adoption experiments demonstrated that the inheritance of ADHD was found between 70 and 90% (Kotte et al. 2013; Thapar et al. 2013), which is as high as other psychiatric disorders like schizophrenia, autism, and bipolar disorder (~75–80%) (Sullivan et al. 2012). Moreover, as ADHD arises due to polygenic genetic background, in which multiple genetic variants contributed, detection of risk genes is challenging (Franke et al. 2009; Gizer et al. 2009).

For the detection of risk genes, genetic studies involved two approaches: (1) hypothesis-driven and (2) hypothesis-free approaches (Table 6.1).

6.3 Psychiatric Comorbidity

Various twin and sibling experiments indicated that about 45% of covariance in genetic factors was found across externalizing, internalizing, and phobia symptoms; 31% in neurodevelopmental symptoms; and 10–36% in psychiatric symptoms (Pettersson et al. 2016; Waldman et al. 2006). The results of two studies demonstrated that 18 and 38% of the SNP heritability of the mother was responsible for internalizing, externalizing, and attention problems (Pappa et al. 2015; Neumann et al. 2016). Few studies found the genetic relations between ADHD and antisocial behavior, substance-abuse, oppositional defiant, and conduct disorders (Nadder et al. 2002; Kuja-Halkola et al. 2015; Capusan et al. 2015). Studies from the USA (Ronald et al. 2010), the UK (Ronald et al. 2008), and Sweden (Ronald et al. 2014) confirmed the genetic overlap in children with ADHD and autism. Genetic overlaps were responsible for the coincidence of internalizing disorders such as attempted and completed suicide with ADHD (Ljung et al. 2014). Experiments indicated the relationship between ADHD and depression, and the coincidence was triggered by

Table 6.1 Detection of risk genes by hypothesis-driven and hypothesis-free approaches (Klein et al. 2017)

Risk genes detected by hypothesis-driven approach (candidate genes and their associates)	Risk genes detected by hypothesis-free approach
Genes coding for dopamine and serotonin transporters (*SLC6A3/DAT1* and *SLC6A4/5HTT*)	A locus on the short arm of chromosome 16—cadherin 13 (*CDH13*)
Genes encoding D4 and D5 dopamine receptors (*DRD4* and *DRD5*)	Latrophilin 3 (*LPHN3*) gene on chromosome 4
Gene for a serotonin receptor (*HTR1B*)	
Gene encoding synaptosomal-associated protein 25, *SNAP25*	
Genes encoding tryptophan hydroxylase 2 (*TPH2*), adrenoceptor alpha 2A (*ADRA2A*), dopamine beta-hydroxylase (*DBH*), and monoamine oxidase A (*MAOA*)	
Genes for *ADRAB2*, *DAT1*, *DRD4*, *TPH2*, and *MAOA*	

shared genetic factors (Faraone and Biederman 1997, 1998). Only a few studies showed the familial link of ADHD to intellectual impairment. A report demonstrated that the intelligence quotient of average individual was nine points greater as compared to ADHD patients (Frazier et al. 2004), and another indicated that the individuals with ID and their relatives were prone to ADHD as compared to peoples without ID and their relatives (Antshel et al. 2006). The involvement of genetic factors in nonpsychiatric comorbidity such as asthma, obesity, and epilepsy was explored (Mogensen et al. 2011; Chen et al. 2017; Brikell et al. 2018).

6.4 Genetic Linkage Studies

Being the earliest genome-wide method, the genetic linkage studies involved searching the DNA segment transmitted within families of ADHD. By involving the Genome Scan Meta-Analysis, Zhou et al. (2008) indicated a significant genome-wide linkage on particular loci (64–83 Mb) of chromosome 16. Most ADHD linkage studies involve the offspring or parents of different people. Arcos-Burgos et al. (2004) studied about 16 multigenerational Colombian families and found the link to chromosomes 4 (4q13.2), 5 (5q33.3), 8 (8q11.23), 11 (11q22), and 17 (17p11) and another region (*LPHN3*). In a study by the International Multisite ADHD Gene project, the analysis of 51 genes from 674 European ADHD families exhibited the overlapping for DAT1, DRD4, ADRAB2, TPH2, and MAOA genes (Brookes et al. 2006).

6.5 Candidate Gene Association Studies

In the beginning, genetic studies of ADHD were associated with the search of genes linked to the cause of ADHD. As ADHD drugs target monoaminergic transmission (dopamine and noradrenaline), many experiments observed "candidate genes" in the pathways. Gizer et al. (2009) indicated that the candidate genes for ADHD included *DAT1*, *DRD4 and DRD5*, *5HTT and HTR1B*, and *SNAP25* and *BAIAP2*I (brain-specific angiogenesis inhibitor 1-associated protein 2 gene). As 3′-untranslated region of *SLC6A3* contains 40 bp variable number of tandem repeats, two variants are formed with 9- (9R) and 10-repeats (10R) due to polymorphism. The 9R allele is connected to adults with ADHD (Faraone and Mick 2010), while 10R allele is for children (Franke et al. 2010) (Table 6.2).

6.6 Genome-Wide Significant Common Variants

Genome-wide association studies (GWAS) examine the whole genome to identify common (greater than 1% of the population) DNA variants having minor etiologic effects. Initial studies on ADHD (Neale et al. 2010; Yang et al. 2013) did not show any genome-wide DNA variant, although about 5000 samples were collected from

Table 6.2 ADHD candidate genes

Name of the gene and protein	Chromosome position	SNP in marker gene
ADRA1B (adrenoceptor alpha 1B)	5q33.3	Six SNPs (rs2030373, rs6884105, rs756275, rs6892282, rs6888306, and rs13162302)
ADRA2A (adrenoceptor alpha 2A)	10q25.2	rs1800544 SNP in the promoter region—G-allele rs553668 SNP in the promoter region—T-allele
ADRA2C (adrenoceptor alpha 2C)	4p16.3	ADRA2C (GT)n repeat polymorphism (STR marker adra2c1)
ADRB1 (adrenoceptor beta 1)	10q25.3	rs10885531
ADRB2 (adrenoceptor beta 2)	5q31-q32	rs17108817
ASTN2 (astrotactin 2)	9q33	C-allele of rs12376789
BCHE (butyryl cholinesterase)	3q26.1–q26.2	rs4680612 and rs829508
BDNF (brain-derived neurotrophic factor)	11p14.1	rs6265
CALY (calcyon neuron-specific vesicular protein)	10q26.3	rs4838721A and rs2275723C
CCSER1/FAM190A (coiled serine-rich protein I)	4q22.1	rs12505502
CDH13 (cadherin 13)	16q23.3	rs11150556
CHRNA3 (cholinergic receptor, nicotinic alpha 3)	15q25.1	rs578776 and rs3743078
CHRNA4 (cholinergic receptor, nicotinic alpha 4)	20q13.33	rs3787138
CHRNA7 (cholinergic receptor, nicotinic alpha 7)	5q13.3	D15S165 and D15S1360 (microsatellite markers)
CNTF (ciliary neurotrophic factor)	11q12	rs550942
COMT (catechol-*O*-methyl transferase)	22q11.21	rs4680
CPLX2 (complexin 2)	5Q35.2	rs7448069
DBH (dopamine beta hydroxylase)	9q34	rs1076150, rs2873804, rs1548364, rs2519154, and rs1108580
DDC (dopamine decarboxylase)	7p12.1	rs3887825, rs3807566, rs7786398, rs10499695, and rs6969081
DIRAS2 (DIRAS family, GTP-binding RAS-like 2)	9q22.32	rs1331503, rs1412005, rs1331503, rs2297354, rs1331504, rs7848810, rs1412005, and rs689687
DRD1 (dopamine receptor D1)	5q34.q35	rs10039221, rs11747728
DRD2/ANNK1 (dopamine receptor D2)	11q22.q23	rs1800496, rs1801028, and rs1799732
DRD3 (dopamine receptor D3)	3q13.3	rs747302, rs1800955
DRD4 (dopamine receptor D4)	11p15	rs4646984 and rs4646983
DRD5 (dopamine receptor D5)	4p16.1	rs6283
FADS2 (fatty acid desaturase 2)	11q12.2	rs498793
FTO (fat mass and obesity associated)	16q12.2	rs8050136

(continued)

Table 6.2 (continued)

Name of the gene and protein		Chromosome position	SNP in marker gene
GDNF (glial cell-derived neurotrophic factor)		5p13.1-p12	rs2910710, rs11111, rs3749692, rs2910797
GPRC5B (G-protein-coupled receptor, class C, group 5, member B)		16p12	rs6497416
GRIN2A (glutamate receptor, ionotropic *N*-methyl-D-aspartate 2A)		16p13.2	rs8049651 polymorphism
GRM5 (glutamate receptor, metabotropic 5)		11q14.3	*rs*7341475
GRM7 (glutamate receptor, metabotropic 7)		3p26-p25	rs3792452
HES1 (Hes family bHLH transcription factor 1)		3q28-q29	rs11689432
HTR1A (5-hydroxytryptamine (serotonin) receptor 1A, G protein coupled)		5q11.2-q13	rs10042486, rs1423691, rs878567
HTR1B (5-hydroxytryptamine (serotonin) receptor 1B, G protein coupled)		6q13	rs6296 and rs6298
HTR1E (5-hydroxytryptamine (serotonin) receptor 1E, G protein coupled)		6q14-q15	rs11962946, rs722763
HTR2A (5-hydroxytryptamine (serotonin) receptor 2A, G protein coupled)		13q14-q21	rs3125, rs7330636
HTR2C (5-hydroxytryptamine (serotonin) receptor 2C, G protein coupled)		Xq23	rs3813929, rs518147
HTR3A (5-hydroxytryptamine (serotonin) receptor 3A, G protein coupled)		11q23.1-q23.2	rs1062613, rs1176744,
HTR3B (5-hydroxytryptamine (serotonin) receptor 3B, G protein coupled)		11q23.1	rs3891484, rs3758987, rs11606194, rs1176746 rs1176744, rs2276307
LPHN3 (Latrophilin 3)		4q13.1	rs6813183, rs1355368, and rs734644
MAOA (Monoamine oxidase A)		Xp11.4-p11.3	rs6323, rs1137070, rs3027407
MAOB	Monoamine oxidase B	Xp11.4-p11.3	rs4824562, rs56220155, rs2283728, rs2283727, rs3027441, rs6324, rs3027440
NOS1	Nitric oxide synthase 1	12q24.22	SNP in exon 1f-VNTR
PNMT	Phenyl ethanolamine *N*-methyl transferase	17q12	rs3764351
PRKG1	Protein kinase, cGMP-dependent, type I	10q11.2	
SLC1A3	Solute carrier family 1, member 3	5p13	rs2269272

(continued)

Table 6.2 (continued)

Name of the gene and protein		Chromosome position	SNP in marker gene
SLC6A2/ NET1	Solute carrier family 6, member 2	16q12.2	rs28386840
SLC6A3/ DAT1	Solute carrier family 6, member 3	5p15.3	rs2937639
SLC6A4/ 5HTT	Solute carrier family 6, member 4	17q11.2	rs140701
SLC9A9/ NHE9	Solute carrier family 9, member 9	3q24	rs13058809, rs1992426, rs4330252, rs6414353, rs6770565, rs7613679
SLC18A2/ VMAT2	Solute carrier family 18, member 2	10q25	rs363256, rs363279
SNAP25	Synaptosomal-associated protein	20p12-p11.2	rs363040, rs363043, rs362584, rs6108463
SPOCK3	Sparc/osteonectin, cwcv and kazal-like domains proteoglycan	4q32.3	rs7689440, rs897511
STX1A	Syntaxin 1A	7q11.2	rs2228607
SYP	Synaptophysin	Xp11.23-p11.22	rs10861968, rs1465044, rs12581451, rs7315638, rs2251214
SYT1	Synaptotagmin 1	12q21.22	rs35459363
TH	Tyrosine hydroxylase	11p15.5	rs3842727
TPH1	Tryptophan hydroxylase 1	11p15.3-p14	rs211102
TPH2 (tryptophan hydroxylase 2)		12q15	rs2129575
VAMP2	Vesicle-associated membrane protein 2	17p13.1	Insertion/deletion polymorphism of 26 bp, referred to as 26 bp Ins/Del

trios (parents and ADHD child), ADHD, and normal children. The molecular landscape obtained from these experiments and with others indicated that genes controlling neurite outgrowth were significantly involved in the etiology of ADHD (Poelmans et al. 2011). Studies conducted later indicated that the pathways controlling the synthesis and release of neurotransmitter, neuronal growth, and formation of axons were responsible for ADHD (Mooney et al. 2016; Aebi et al. 2016).

A cluster of ADHD researchers completed a GWAS meta-analysis involving about 20,000 ADHD patients and about 35,000 controls (Demontis et al. 2017). Among the 12 genes, *FOXP2* (controls dopamine levels in ADHD-linked brain regions) was specifically distinguished as earlier experiments indicted their involvement in adult ADHD. In addition, Demontis et al. (2017) indicated various genome-wide significant loci such as *DUSP6* as a regulator of dopamine levels in the synapses, *ST3GAL3 and MEF2C* as the mutant forms found in ID and other psychiatric disorders, *SEMA6D* as a regulator of neuronal wiring, and *LINC00461* to be responsible for educational attainment.

6.7 Common Variant ADHD as a Polygenic Disorder

The GWAS indicated that the inheritance of ADHD could be due to the polygenic role of numerous variants having low effects (Faraone et al. 2005). The polygenic score of ADHD was established by quantification of ADHD risk scores in a single-sample subset and viewing that in a dose-dependent manner of validation subsets of ADHD. Martin et al. (2014) reported the genetic overlap between ADHD and ASDs, which was confirmed by twin study data (Ronald et al. 2014; Polderman et al. 2014) and gene set analyses (Bralten et al. 2018). Other polygenic studies also confirmed the genetic overlap between ADHD and conduct disorder (Faraone et al. 1991, 1997), schizophrenia and bipolar disorder Larsson et al. (2013), and depression (Faraone et al. 1991). The polygenic risk of ADHD (Demontis et al. 2017) was highly correlated with about 220 disorders and traits, including IQ, lung cancer, coronary artery disease, neuroticism, obesity, depression, smoking, school achievement, and cross-disorder GWAS. The GWAS by Cross-Disorder Group of the Psychiatric Genomics Consortium (2013), analyzed children with psychiatric disorders (bipolar disorder, autism, schizophrenia, and major depressive disorder) with ADHD and indicated the presence of genetic overlap among the ITIH3, CACNA1C, AS3MT, and CACNB2 with ADHD children.

6.8 Rare Variants and Genetic Syndromes

Numerous chromosomal aberrations were present in ADHD children and other developmental diseases (Williams et al. 2012). FMR1 is a gene encoding an RNA-binding protein, and its diminished function leads to mental retardation (fragile X syndrome). The patients suffered from enhanced glutamatergic transmission and diminished GABA signaling. A study by Lo-Castro et al. (2011) indicated that about 31.5%, 7.4%, and 14.8% belonged to inattentive, hyperactive, and combined type, respectively, and were affected by FXS. The locus of neurofibromin 1 (NF1) is found in chromosome 17q11.2, whose mutation leads to the skin, CNS, and eye tumors. About 33% of children who are affected by nonfunctional NF1 presented with ADHD symptoms (Kayl et al. 2000). The pathological connections between ADHD and NF1 might arise due to the damage in basal ganglia.

In children affected by tuberous sclerosis complex (genetic disease linked to brain tumor, reduced development, skin abrasions, and benign tumors of other organ systems, having epileptic seizures and cognitive impairment), Turner syndrome and Klinefelter syndrome, Williams-Beuren syndrome (microdeletion on chromosome 7 and linked with symptoms such as elf-like facial expression, pulmonary and cardiovascular abnormalities), and DiGeorge syndrome (22q11 deletion), the prevalence of ADHD is as high as about 60% (Leyfer et al. 2006; de Vries et al. 2006; Bruining et al. 2010; Hoeffding et al. 2017).

The sentence is corrected as Martin et al. (2015) indicated that the presence of rare single-nucleotide variants (SNVs) (0.3–1% of the entire human DNA) containing polymorphisms of a base pair and copy number (CNVs) was responsible for the role

of heredity in ADHD. An experiment involving about 2800 ADHD children found an increase in CNVs in locus 15q13.3 (Williams et al. 2012) and another in 16p13.11 (Williams et al. 2010). Few genome-wide screening studies demonstrated that the deletion in the gene coding for neuropeptide Y on chromosome 7p15.2–15.3 (Lesch et al. 2011) and GRM5, 7, and 8 (coding for glutamate receptor, metabotropic 5, 7, and 8) (Elia et al. 2012) was found in ADHD children.

6.9 Diagnosis and Therapeutic Approaches to ADHD

Lesions in the dopaminergic and noradrenergic neuronal pathways (reduced volume and activity of related brain areas) and their dysfunction have been reported to underlie ADHD behavior such as attention, emotion, and behavior (Heyer and Meredith 2017). Genetic studies indicated that ADHD is not only a simple "catecholaminergic" disease but a multifactorial disease which involved the abnormality of various processes including "neurite growth," "synaptic plasticity," and/or "glutamatergic signal transmission" (Demontis et al. 2018). Another new approach in the application of genetics is prediction, also known as pharmacogenomics. Presently, therapy is primarily dependent upon the enhancement of the dopaminergic neurotransmission. Therefore, more effects of genes concerned in the arbitration of dopaminergic effects could be anticipated. Few studies indicated that polymorphisms in genes of dopaminergic neurotransmission or synapse could lead to stimulant therapy.

6.10 Future Directions in Genetics Research

Until recently, conflicting and unsatisfactory results were obtained from the genetic studies. Although the role of inheritance is considered in ADHD, most of the linkage studies did not indicate wide-ranging overlaps, except few meta-analyses. As ADHD is regarded as a multi-genetic disorder, less knowledge about the genetic component of ADHD was shown by candidate gene-based experiments. GWAS carried out initially did not show any significant changes; however, the findings of studies done later redirected future ADHD research to the novel gene systems and processes. In general, GWAS in psychiatric disorders, including ADHD, were found to be poor (demonstrated less than 10% of variants) as compared to other multifactorial disorders because (1) these are complex and multi-genetic diseases that can be diagnosed with studies involving a large population; (2) the interaction of gene with other genes and environment plays a heavy role in the inheritance; (3) apart from variations in the SNPs found in the majority of experiments, commonly occurring changes in DNA structure (insertions, deletions, and duplications) were less studied; (4) the effect of rare genetic variants in the cause of ADHD is more than the expected; and (5) it is difficult to correlate the clinical diagnosis of psychiatric disorders with the genetic studies.

6.11 Conclusions

Association between the genetic experts (researchers), clinicians, and statisticians is needed in future for the identification of more novel ADHD genes. As the low-frequency gene variants were linked with the inheritance of individual patients, their detection might pave the way for accepting their functions and finding the relationship between each gene to symptoms and pathology. It will lead to the development of prediction and prevention strategies for diagnostic purposes or therapeutic strategies.

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