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Review Article
Genetic diversity of Attention-Deficit/Hyperactivity Disorder

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable neuro developmental disorder. Traditionally ADHD was considered a childhood disorder but recent evidence confirms that ADHD can also occur in adulthood. The prevalence of ADHD worldwide is around 5% in children and 3% in adults. ADHD affects patients throughout their lives by causing failures in education as well as in occupations, which increase the risk of accidents and criminality. The disorder has no single cause, which reflects the heterogeneity of ADHD. Understanding the genetic and molecular changes associated with familial/heritable ADHD development is challenging, due to the lack of relevant models of ADHD and the difficulty of collecting brain samples. The current review will highlight upon the genetic diversity of ADHD and summarize some recent relevant studies. Knowledge about the ADHD's variants might be useful for a new ADHD genetic research.

Key words: Genetic, ADHD, diversity, variants, neuro developmental disorders, epigenetic mechanisms and genome-wide association

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a complex heterogeneous disorder that is defined as a continual, trans-situational type of hyperactivity or inattention or both, that interferes with a person's normal functioning and is inappropriate to the stage of development[1]. ADHD is one of the most common neurodevelopmental disorders in children and was viewed as a childhood condition until the end of the 20th century, when it was convincingly shown to exist also in adults[2,3]. This disorder negatively affects different aspects of the patient's family, education and society and it increases expenditures related to health services, injuries, substance abuse, traffic accidents, suicide, criminality and divorce[4,5].

The symptoms among patients vary throughout development as the behavior of very young children shows hyperactive impulsive symptoms, while middle-aged children display inattentive behavior. During adolescence and adulthood, the symptoms involve a persistence of inattention and a decrease in hyperactivity[6,7]. The age of onset of symptoms was typically before the age of 7 years according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) but has been modified to before the age of 12 in DSM-5. A diagnosis of ADHD is made based on the presence of six or more hyperactive or hyperactive/impulsive symptoms as well as a full history of development and gestation[8]. The symptoms of ADHD are varied as both impulsive behavior and hyperactivity seem to decline, while inattention continues with age[9]. In terms of gender differences, boys are diagnosed with ADHD more than girls[10]. The prevalence of ADHD worldwide among children is around 5.3-6.5% while in adults it is between 2.5-3.4%[11,12].

The etiology of ADHD effects on the function and structure of the brain is implicated by environmental risk factors and genetics. The environmental risk factors include prenatal, pregnancy and birth complications (including preterm birth) as well as maternal smoking, obesity and alcohol consumption[13-16]. Furthermore, ADHD is a complex heritable disorder that runs in families as indicated by reports showing that a first-degree family member relative to a proband with ADHD has a 5-10-fold increased risk of having ADHD compared to members of a normal healthy family[17-19]. The concordance rate is also higher among monozygotic twins compared to dizygotic twins[20]. An adoption study also showed that the rate of ADHD is higher in patients' biological parents than in their adoptive parents[21]. Therefore, strong evidence supports a genetic contribution to ADHD, with a heritability estimation between 70 and 80%[20,22].

ADHD genetic diversity: ADHD is a heritable psychiatric disorder and genetic risk factors significantly influence its pathogenesis, with single nucleotide polymorphisms (SNPs) contributing around 22% of the phenotypic variance[23]. DNA methylation is an epigenetic mechanism that is significant in its development, differentiation of cells and neurogenesis regulation. However, epigenetic alterations to this process lead to various neurodevelopmental disorders, including ADHD, borderline personality disorders and autism spectrum disorders[24]. The structure and functioning of the brain are influenced by genetic factors and altered circuits that affect movement and coordination, memory, learning and motivation lead to the development of abnormal behaviors and neuro developmental diseases such as ADHD. For instance, the research by Hibar *et al.*[25] that investigated how genetic variants alter the structure of key brain regions showed that they affected the volumes of the caudate nucleus and putamen. These regions are involved in regulating movements, learning, memory, rewards, emotions, motivations and romantic interactions and are crucial in the degeneration of neurological and neuro developmental functions, leading to disorders such as Parkinson's disease and ADHD, respectively. Markedly, the identification of these genetic variants and their effects on the functioning of the brain enables the determination of neuropsychiatric dysfunction while providing insights into the causes of their variability. Indeed, Xu *et al.*[24] showed that multiple epigenetic factors predict the occurrence of ADHD as these influence key functions of the brain, including sensorimotor functions, emotions, attention and cognition.

In their study, the researchers aimed to use the epigenetic factors to establish an ADHD prediction model, using a population of Chinese children. They carried out pair-matching case controls and children with ADHD underwent further evaluation using structured diagnostic interviews. The caretakers of children with ADHD were also interviewed using the Diagnostic and Statistical Manual of Mental Disorders-revised[24]. Besides, the researchers assessed the promoter methylation levels in the children with ADHD as well as those of the risk genes including DRD5, DAT1 and DRD4 and the expression profile of MYST4, MeCP2, p300 and HDAC1 genes that are involved in the modification of histones. The prediction models were established using the multivariate logistic regressions. The results showed that all the identified genes were risk factors for developing ADHD, although the methylation of DRD4, an upstream gene, altered its transcription and was, therefore, involved in ADHD development[24]. Also, the histone acetylation and aberrant

DNA methylation predicted the development of ADHD. However, the study only focused on Chinese children, which reduces the generalizability and transferability of the results. Nonetheless, it highlighted the association of epigenetic markers and ADHD, indicating the various genes involved in the development of ADHD and its diversification.

In another study, Pineda-Cirera *et al.*[23] carried out a study to evaluate how Allele-Specific Methylation (ASM) contributes to ADHD development and the epigenetic mechanisms involved SNPs and their correlation with the levels of DNA methylation at CpG sites. The researchers used 3896 tag SNPs in influencing the methylation of the DNA in various regions of the human brain. They conducted a case-control association study using a large Genome-Wide Association Study (GWAS)[23]. Markedly, GWAS enables the identification of novel risk variants and indicates their effects. The genetic variants identified by genome-wide association studies show the proportion of heritability of genes and the associations below their current thresholds. The results by Pineda-Cirera *et al.*[23] indicated that the genetic variants of ADHD arise and are enriched with ASM-SNPs that are correlated with methylation in the CpG sites in the promoter regions. Notably, DNA methylation affects the translation and expression of genes and the researchers investigated the effects of the ASM SNPs in high linkage disequilibrium in brain tissues. They noted that the expression of ARTN, PIDD1 and C2orf82 genes was altered. Further, these genes resulted in varying genetic variants of ADHD depending on their affected expression and the variants of C2orf82 correlated with the brain volumes. The researchers concluded that the differential cis-methylation influences the development of genetic variants in ADHD and these affect the epigenetic regulation and expression of genes and brain volumes. The study also used a large sample of tag SNPs, 3896 and a large GWAS sample of 20000 cases and 35000 controls, which increases the generalizability and transferability of the results. However, the researchers did not carry out a follow-up study to evaluate the findings in an independent sample. Also, Pineda-Cirera *et al.*[23] only considered the ASM variants that are common and did not include the non-cis ASM variants that are rare. Therefore, the study may not be representative.

In another study, Hawi *et al.*[26] conducted a case-control GWAS to evaluate the genetic variants of ADHD associated with the tenascin R (TNR) gene. The researchers used a hypothesis-free GWAS design and used a study population of 480 ADHD cases and 1208 controls. The DNA samples collected were genotyped and input into the reference panel. The SNPs were identified following quality control and pruning of the genotypes. Logistic regression analyses were used to indicate the association between the case-control status and the SNP. The Polygenic Risk Score (PRS) the researchers carried out showed that the genetic risk of ADHD defined the status of the patient. The results showed a genome-wide significant association of ADHD and the Tenascin R gene, indicating a genetic variant of the ADHD disease[26]. Notably, members of the Tenascin family are extracellular matrix glycoproteins involved in physiological processes such as the modulation of the sodium ion channel, neural cell adhesion and embryogenesis. Genetic association studies have also implicated the gene in other brain disorders, such as neurological sleep disorder, Alzheimer's and narcolepsy[27]. However, the study has limitations, including a relatively small sample size, which reduces its statistical power and the generalizability and transferability of the results. Nonetheless, the study showed the genetic variant of ADHD associated with the TNR gene.

Stergiakouli *et al.*[28] also carried out a study to investigate the influence of common genetic variants on the pathogenesis of ADHD and indicate the genetic variations using GWAS. The authors analyzed the genome-wide SNPs in 727 children with ADHD and 5081 controls. The gene sets identified were tested for an excess of genes and the rare Copy Number Variants (CNVs) were indicated. The GWAS carried out did not indicate any SNPs and the rare CNVs were more in the case studies than the controls. However, the researchers noted an overlap of three biological pathways that were enriched with SNP association and these included the cholesterol-related and the CNS development pathways[28]. In particular, the CHRNA7 gene, a member of the nicotinic acetylcholine receptor family, was implicated in the pathogenesis of ADHD and was noted in a large number of case studies. The researchers concluded that the rare genetic variant, CHRNA7, is relevant to the pathogenesis of ADHD[28]. However, the researchers used a small sample size of only 727, which reduces the statistical power of the research and the generalizability and transferability of the results. Also, the use of GWAS and CNV in the study only permitted identifying a percentage of the genetic variations and the effects of environmental and genetic factors were not evaluated. Similarly, Williams *et al.*[29] noted the role of CHRNA7 and rare duplications in the pathogenesis of ADHD variants. In their study, Williams *et al.*[29] conducted GWAS of large and rare CNVs in 896 children with ADHD to recognize the rare CNVs that are important in the pathogenesis of ADHD. They used 2455 controls. Their results indicated 1562 rare CNVs that were

more than 100 kb in size and these were separated into 912 independent loci. They noted that duplications in the CHRNA7 gene at chromosome 15q13.3 were consistent in the case subjects, indicating that the gene has a significant role in the pathogenesis of ADHD. Although the study indicated CHRNA7 as a novel risk factor for ADHD and a genetic variant of the disease, the researchers did not assess its inheritance. Also, the study is not suited for the indication of phenotypic variation, highlighting the need for larger studies with variabilities in the phenotypes.

Sanchez-Mora *et al.*[30] carried out GWAS using 607 cases and 584 controls to indicate the influence of the FBXO33 gene in the development of ADHD. The top signals were evaluated in a replication study of 2104 cases and 1901 controls. Markedly, none of their findings went beyond the threshold of the genome-wide threshold to be indicated as significant. However, a novel gene, the FBXO33 gene, was noted in the gene-wise analyses. The FBXO33 gene is a member of the F-box gene family that encodes a leucine-rich repeat in the placental RNAse inhibitor. This gene's variations were associated with reduced expression of the lymphoblastoid cell lines and reduced volume of the frontal gray matter[30]. However, the research did not evaluate the specific mechanism of the genetic variations in the development of the neurodevelopmental disorder, highlighting the need for more studies that use large study populations.

SLC2A3 gene that encodes the glucose transporter-3 (GLUT3) and has a role in cerebral glucose metabolism has also been implicated in the development of ADHD. It is important in the excitation of the cerebral neurons and modulation of the excitatory-inhibitory balance. Merker *et al.*[31] conducted case-control association analyses of SL2CA3 SNPs and CNVs to provide additional functional and genetic evidence on the role of the gene in the dysfunction of the GLUT3 in ADHD. The samples involved were 1886 and 1692 case studies for SNP and CNV against 1988 and 1721 controls, respectively. The gene expression was assessed in peripheral cells during neurocognitive tasks[31]. The results showed elevated expression of SLC2A3 mRNA in peripheral blood cells and changed potentials, indicating that there were deficits in both the cognitive response and working memory in duplication carriers. Merker *et al.*[31] concluded that the rare variations of SCL2A3 affect the utilization of cerebral and neuronal glucose and the homeostasis of energy, resulting in neuro cognitive deficits that lead to ADHD. Like wise, Neale *et al.*[32] conducted case-control GWAS of ADHD to identify the genetic variants that influence the traits at a genome-wide level. They used 896 cases and 2455 controls. All study samples were screened for bipolar and psychotic symptoms before they were genotyped and analyzed using a generalized linear model. Their results indicated the lack of genome-wide significant associations. However, various genes were indicated as risk variants for the development of ADHD. These genes included FLNC, CDH13, NXPH1, PRKG1, PPMH1H, HK1 and HKDC1[32]. These genetic variants are small and rare. However, the research by Neale *et al.*[32] used a small study sample of 896 cases and this reduces the generalizability and transferability of the results, while highlighting the need for more studies that use large sample sizes to establish the roles of the identified genetic variants in the pathogenesis of ADHD. In another study, Lionel *et al.*[33] sought to identify the de novo and rare CNVs in 248 unrelated ADHD patients and 2357 controls. The researchers identified the rare CNVs in case studies that were not present in the controls and used microarrays to evaluate their independence. Their results indicated that deletions of ASTN2 and TRIM32 neuronal genes had a strong association with ADHD. However, other genes, including MACROD2, CHCHD3, DCLK2, SORCS3 and SORCS1, were thought to have a role in the etiology of the disorder[33]. These genes were absent in the controls of the study but present in the case studies, confirmation of the existence of underlying susceptibility genes for various neuropsychiatric disorders. However, the results by Lionel *et al.*[33] were based on a small study sample of 248 and this reduces the statistical power as well as the generalizability and transferability of the results.

In another study, Lesch *et al.*[34] conducted genome-wide CNV analysis in 99 children and adolescents with severe ADHD to indicate the micro-duplications and micro-deletions that may have a role in the development of the disease. Potential syndrome-associated CNVs were identified using high-resolution array comparative genomic hybridization and these were 13 duplications and four deletions[34]. Most of these mutations occurred de novo. These candidate genes express BCHE in chromosome 3q26.1 and had a deletion and PLEKHB1 that functions in the primary sensing neurons in chromosome 11q13.4 and had a duplication[34]. The other aberrant genes that were noted to influence the occurrence of ADHD and formed the genetic variants of the disease included the NADHD dehydrogenase 1α sub-complex assembly factor 2 (NDUFAF2), the neuronal glucose transporter 3 (SLC2A3) and the brain-specific phosphodiesterase 4D isoform 6 (PDE4D6)[34]. Notably, other studies that have been carried out before have shown the influence of the SLC2A3 gene in the development of ADHD, including the studies by Merker *et al.*[31]. Lesch *et al.*[34] concluded that the CNVs of rare behavior-related

genes are significant in developing ADHD, particularly. The research by Lesch *et al.*[34] is important in highlighting the influence of CNVs of rare behavior-related genes in the development of ADHD.

In another study, Arcos-Burgos *et al.*[35] indicated a variant of the latrophilin-3 gene, LPHN3, in ADHD. The researchers integrated various functional and statistical approaches to identify the novel genes that contribute to the development of ADHD by using a population isolated from a large multigenerational family of 2627 ADHD cases and 2531 controls. Arcos-Burgos *et al.*[35] then performed brain imaging to indicate the functions of the identified genes. Their results indicated that LPHN3 variants were expressed in key brain regions that control the attention and activity of individual, neuronal metabolism and the response to stimulating medications[35]. Markedly, the functioning of these variants increased the susceptibility of individuals developing neuropsychiatric disorders such as ADHD. The researchers concluded that ADHD is linked and associated with the variations of LPHN3, a novel candidate gene and forms a genetic variant of the disease[35]. The study results were based on a large number of case studies, which increases the generalizability of the results to another population. However, the ADHD cases used in the study were isolated from multigenerational families and this reduces the transferability of the results. This is because the novel candidate gene identified, LPHN3, could be inherited from ADHD parents and the researchers did not evaluate whether the variant gene is inherited or occurred de novo. Similarly, a replication study by Ribases *et al.*[36] indicated the LPHN3 gene as a genetic variant of ADHD. The researchers used genetic isolates from families of four different populations and conducted a case-control association study in 334 adult patients with diagnosed ADHD and 334 controls. The results indicated single- and multiple-marker analyses and the association of the LPHN3 gene and ADHD was consistently noted[36]. LPHN3 gene belongs to the G-protein coupled receptors and is expressed in the amygdala, cerebral cortex, cerebellum and the caudate nucleus. The study results support the contribution of the novel gene in the development of ADHD, thereby forming a genetic variant. However, the case-control association study was based on a small study sample size of only 334 individuals from four populations. This reduces the statistical power of the results and their generalizability and transferability, highlighting the need for more studies that use a large population size. Likewise, the study by Fallgatter *et al.*[37] evaluated the role of LPHN3 in the development of ADHD. The researchers used 216 cases of ADHD to evaluate the influence of the genetic variations of the LPHN3 gene. The study participants completed a Continuous Performance Test (CPT) while simultaneously undergoing an electrocardiogram. The results showed that individuals with omission errors of the two copies of the gene had altered behaviors and reduced neurophysiological measures that were consistent with ADHD[37]. However, the results were based on a small study population, highlighting the need for more studies that use large population sizes to indicate the role of the gene in ADHD.

Puentes-Rozo *et al.*[38] carried out a study to evaluate the genetic variations underpinning the risk of ADHD in a Caribbean community. The researchers genotyped 26 SNPs in genes that have been shown to have a role in developing ADHD, including SNAP25, ADGRL3, SLC6A2, DRD4 and FGF1. They investigated their association in 386 individuals with ADHD who belonged to 113 nuclear families[37]. The study participants were identified from a Caribbean community and family-based association tests were used to classify them. The results by Puentes-Rozo *et al.*[38] indicated that the variants of ADGRL3, FGF1 and SNAP25 had a role in the development of ADHD. This study can be used to indicate and predict the susceptibility of the Caribbean community to ADHD. However, the results cannot be transferred to other populations as the study population was exclusively from one community. Also, the study sample of 386 individuals is small and there is a need for more studies using a large and inclusive population to ascertain the role of these variants in the development of ADHD.

Zayats *et al.*[39] also carried out a genome-wide analysis of ADHD to identify the genetic variations of the disease in an ethnically homogenous Norwegian population. The study participants were identified through Norwegian medical and birth registries and individuals with confirmed diagnoses of ADHD were selected. Genotyping was carried out and statistical analyses were used to indicate the identified genetic variations and ADHD associations. GWAS, SNP-heritability tests and gene-based association tests were also carried out[39]. The study included 135 ADHD cases and 880 controls. Genes involved in the control of inflammation, cell adhesion and gene expression were associated with the development of ADHD. In particular, SNPs at the ENSG00000263745 and SLC9A9 genes were associated with the disease[39]. Similarly, the GWAS by Markunas *et al.*[40] identified SLC9A9 as a candidate genetic variation in the development of ADHD. Notably, the studies confirmed the genetic variations of the ADHD disorder and indicated targets for further studies. However, the study sample size was small and reduces the generalizability and transferability of the results.

CONCLUSION

To sum up, this literature review focused on identifying the genetic variants of ADHD. The disorder is a heritable psychiatric disorder and epigenetics that influence the key functions of the brain, including memory, rewards, motivations, learning, emotion and cognition, have a role in its development. This literature review showed that there are many genetic variations of the disorder. However, there is a need for more studies using large population sample sizes to be carried out to indicate the roles of these genes in the development of the disorder.

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