Attention deficit and hyperactivity disorder (ADHD): Overview of Gender differences, Genetic, Epigenetic, and Non-genetic aspects

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Abstract

Attention deficit and hyperactivity disorder (ADHD) is a common neurodevelopmental disorder. Around 2.8% of the adult population is affected by ADHD. There are various factors that contribute to the development of ADHD which can be differentiated based on its mode of transmission. Some factors are manifested through inheritance and some are categorized as epigenetic. However, it is quite challenging to determine a well-described cause that contributes to the development of ADHD. Furthermore, there are significant differences between affected men and women. One of the most noticeable differences being that cognitive flexibility and verbal fluency are the qualities that are more evident in male counterparts, whereas for the female counterparts, working memory and inhibition are the qualities that are prominent. This review focuses on the manifestation of ADHD as well as the epigenetic, genetic, and non-genetic factors influencing it. The review also aims to draw attention to the variations between ADHD-diagnosed men and women. The knowledge of the myriad of factors that influence ADHD could be vital in designing efficient and effective therapeutics against this condition. In addition, the differences between men and women could also be exploited to understand the development of ADHD for improved and personalized remedies.

Keywords: ADHD, Neurodevelopmental disorder, Genetic factors, Epigenetics, Therapeutics

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1 INTRODUCTION

Attention deficit and hyperactivity disorder (ADHD) a common neurodevelopmental/neurological disorder. The earliest mention of ADHD was in 1798 when Sir Alexander Crichton noticed a certain disorder wherein the individual found it difficult to focus on their work and was easily distracted (1). ADHD is characterized by being heterogeneous and multifactorial (2; 3; 4). It is a collection of symptoms like lack of attention, persistent distraction, hyperactivity, and impulsivity. This condition is seen in people of all ages where the symptoms typically begin in childhood.

ADHD has a major impact on individuals' social lives, academic performance, habits, and emotional behavior. Kids with this disorder are known to often have side effects that impact their lifestyle. These side effects usually include low performance in academic and work life (5). In adolescence, though there could be a decrease in certain symptoms, individuals often struggle with inattention, impulsiveness, restlessness, and aggressive behavior (6). Adults face issues regarding their efficiency and performance in their work life, as their impulsiveness, inability to be punctual, and difficulties in keeping up with their work would interferes with their daily life. Therefore, since ADHD has a lot of impact on the daily lives of children and adults, it is important to understand the factors affecting the development of ADHD.

This review focuses on the various manifestations of ADHD as well as the epigenetic factors influencing it. The review also aims to draw attention to the genetic variations between ADHD-diagnosed men and women. The goal is to comprehend the disorder and understand the need for a targeted diagnosis.

2 FACTORS AFFECTING ADHD

One of the significant features of ADHD is that it is heterogeneous and multifactorial. To understand the fundamentals of genetic aspects of ADHD, it is important to understand that different genes have different effects. Furthermore, these effects vary in different families and individuals, and there is heterogeneity for these diverse genes (7). ADHD may be brought on by various neurobiological and environmental factors that interact and function in a very complicated way. Though this disorder has contributions from both genetic and environmental factors, the major contributors to the development of ADHD are the genetic factors (4). ADHD is classified as a polygenic trait as multiple genes are involved in the inheritance of this disorder (8). According to previous studies, this disorder has a heritability rate of around 80 percent (4; 9; 10) and around 105 genes have been found to be linked to ADHD (3).

2.1 GENETIC FACTORS

2.1.1 *INHERITANCE AND CONTRIBUTION OF CERTAIN GENES (DRD4 AND DAT1 GENE*

Dopamine transporter genes (DAT1 gene) and dopamine receptor gene (DRD4 gene) are present in humans. While DAT1 is mostly expressed in the basal ganglia and preferentially affects caudate volume, DRD4 is primarily expressed in the prefrontal cortex and preferentially

affects prefrontal grey matter volume (11; 12). Although the DAT1 and DRD4 genes have both been associated with ADHD, DAT1's molecular association is less compelling than DRD4's. The DRD4 gene is typically present in 3–5 copies in most persons. Yet, it appears that those who have ADHD have more copies of the gene (around 7 or more repeats) (9). The number of copies of the gene is significant and affects how the gene functions since it varies the length of the protein it produces and, as a result, how the brain functions. The exact molecular mechanism behind the manifestation of ADHD through genes is still a topic under research however, multiple genes are known to contribute into the progression of ADHD which is discussed further on.

2.1.2 *MUTATIONS*

The occurrence of this disorder is also possible through new (de novo) mutations in the genes of the infant or child that are not seen in the genome of their parents. Some studies state that mutations are the major cause of at least 10% of ADHD cases. Most human beings are exposed to mutation-causing agents most of the time. Therefore, even if an individual does not have ADHD, however, due to mutations that could occur throughout their lifetime, the offspring could have the possibility to develop ADHD (9).

2.1.3 *THROUGH GENE-BY-GENE INTERACTION*

The chance of developing the condition is slightly increased if only one risk gene for ADHD is present. However, when a second or third ADHD risk gene is present, the impact of each gene is amplified to the point where the risk is substantially greater than the simple additive effect of each gene. The study of gene-gene interactions in ADHD, however, is still in its early stages.

2.1.4 *THROUGH GENE-ENVIRONMENT INTERACTION*

It is well understood that people with ADHD have some genes related to the development of ADHD. However, the expression of these genes could be increased because of interaction with certain environmental factors that further might increase the risk of ADHD. For example, maternal alcohol (or tobacco) consumption during pregnancy increases the risk of ADHD by 2.5 times more than that of the general population (9). The development of the disorder depends on the presence of a certain number of risk genes and their expression, which in turn can be influenced by the environment.

2.1.5 *EPIGENETIC FACTORS*

The environment or other factors like malnutrition, chronic stress, etc. interact with the genes involved in ADHD, which further alters or influences the extent to which epigenetic tags are placed in the genes. Currently, researchers have noticed that genetic and environmental factors act together to cause the onset rather than acting separately. The mechanisms underlying this interaction are still unknown, but epigenetic modifications are quickly becoming one of

the most researched pathways for explaining the complex etiology of neurodevelopmental disorders, in which environmental factors can cause gene expression modulation without causing any changes to the DNA sequence (13).

2.1.6 *INFLUENCE OF CERTAIN CHROMOSOMAL DISORDERS*

Sometimes, the development of ADHD can be influenced by alterations in the chromosomal structure like duplication, deletion, or even major damage **(Table 1).**

TABLE 1
Some chromosomal disorders and their association with ADHD

Name of the disorder	**Association with ADHD**	
1. Down's syndrome	a. According to Ekstein S, et. al (2011), children with Down's syndrome have a higher risk of ADHD with the frequency of 43.5%. Some of the symptoms in Down's syndrome are like that of ADHD. b. According to Capone et al., (2006), Myers and Pueschel, (1991) and Cooper et al., (2009) there is an association between Down's syndrome and ADHD which can be explained by the fact that these two conditions are regarding the neural aspect of the body and tend to alter the child's development	(14) (15; 16; 17)
2. Velocardiofacial Syndrome	a. Velocardiofacial syndrome is a hereditary disorder. Children with this disorder are commonly unidentified if there is no notice of any cardiac abnormalities. b. Therefore, according to a study, it is recommended that a child with hyper nasal speaking and could be diagnosed with ADHD would benefit from a facial examination by a psychiatrist.	(18)
3. Williams Disease	a. Kids with this disorder are often seen with problems regarding their learning ability, social and adaptive skills, hyperactivity or communicating. b. These symptoms are quite like that of ADHD. c. According to Rhodes et al., (2011), children with the Williams disease and ADHD have similarities in their neuropsychological functioning and their memory functioning.	(19)

2.2 NON-GENETIC CAUSES

Apart from genetic causes, other non-genetic factors are involved in the development of ADHD. For instance, neurodevelopmental influences of genomic imprinting have made it evident that their contributions to the structural and physiological variations modulate the cognitive and pathophysiological aspects of ADHD.

2.2.1 *NEUROLOGICAL CONTRIBUTIONS*

At times, certain neurological contributions could be the cause of the development of ADHD. For example, certain brain injuries or maldevelopment of the brain alone, where some factors damage the development of certain areas of the brain such as the basal ganglia, cerebellum, and prefrontal cortex, are also linked to the development of ADHD. Maternal malnutrition or medical disorders such as diabetes, etc., are also likely to be the major reason for around 15-25% of ADHD cases.

2.2.2 *CONTRIBUTION THROUGH OTHER FACTORS AFTER BIRTH (DAMAGE ON THE BRAIN, EXPOSURE TO CHEMICALS, DEFICIENCY OF NUTRIENTS, ETC.)*

Sometimes some certain conditions that occur after the birth of an individual can also have an effect, such as tumors, strokes, head trauma, lead poisoning in the initial years of life, or maybe even low levels of nutrients like iron, etc. These, however, account for only 5-10% or less of the total ADHD cases.

3 GENES INVOLVED IN THE MANIFESTATION OF ADHD

3.1 DAT1 GENE

DAT1 is found on chromosome 5p in a recurrent linkage hotspot (7). DAT1 is a dopamine transporter that has been linked to ADHD genetics with a high degree of certainty. Many genetic association studies have been conducted on this, and it is also included in five of the most frequently investigated polymorphisms that have been subjected to meta-analyses (20; 21; 22). Some studies suggest that there are relationships between endophenotypes and the gene. However, more research needs to be carried out to define the role of DAT1 on ADHD (23; 24; 25).

3.2 MONOAMINE RELATED GENES

Many monoamine-related genes have been linked to ADHD. These include dopamine beta-hydroxylase (DBH), D4 dopamine receptor (DRD4), D5 dopamine receptor (DRD5), serotonin 1B receptor (HTR1B), and synaptosomal associated protein 25 isoform (SNAP25) (26).

3.2.1 *THE DOPAMINE D4 RECEPTOR (DRD4*

In a comparison population sample, Ebstein et al. (1996) first reported an association between an exon 3 VNTR (Variable Number of Tandem Repeats) in the DRD4 gene and novelty seeking (a personality trait where there is excitement in response to novel stimuli) (27). Two to eleven 48-bp repeats make up the VNTR. The most common alleles have two, four, or seven repetitions. Alleles with six or fewer repeats are considered short, whereas those with seven or more repeats are considered long. It has been observed that the seven repeat (7R) allele is functionally distinct from the typical shorter alleles. This gene is often expressed in the brain, majorly in the prefrontal cortical regions and it is noticed to be involved in executive

control in people affected by ADHD (28). (Executive control is a set of functions in an individual such as critical thinking, intelligence, etc. that affects and alters their thoughts, foundation for their behavior and action, etc.)

3.2.2 *THE DOPAMINE D2 RECEPTOR (DRD2*

Many genetic association studies as well as a linkage study have conclusively linked this gene to alcoholism (29). However, DRD2 may be linked to antisocial psychopathic personality traits rather than alcoholism per se, according to a recent genetic association study (30). Some studies suggest that people with ADHD tend to have a higher number of dopamine receptors (including the DRD2 gene) in their brain compared to a normal individual. Thus, individuals with ADHD are more susceptible to alcohol, caffeine, or drug addiction.

3.2.3 *DOPAMINE BETA-HYDROXYLASE (DBH*

Gizer et al. (2009) identified a trend toward a connection between the DBH A2 allele and ADHD in a meta-analysis of six studies (31).

3.2.4 *THE SEROTONIN 1B RECEPTOR (HTR1B*

Paternal over-transmission of the HTR1B G861 allele to children with the inattentive ADHD subtype was found in 12 multi-generational Centre d'Etude du Polymorphisme Humain (CEPH) pedigrees with 229 families of ADHD probands. A haplotype block encompassing the gene was found to be associated with the inattentive ADHD subtype. However, after multiple testing was adjusted, three polymorphisms in this block that were nominally associated with this subtype were no longer found to be significantly associated with ADHD (32).

3.3 ADRA2A AND ADRA1A GENES

ADRA2A (adrenoceptor alpha 2A) and ADRA1A (adrenoceptor alpha 1A) genes encode for receptors that are present throughout the central nervous system and the peripheral system. Studies have shown that the variations of these genes are linked with the effectiveness of methylphenidate. Methylphenidate is a medication used to treat ADHD and boosts catecholamine production by activating alpha 2A adrenergic receptors (4; 33).

3.4 THE TACHYKININ RECEPTOR (TACR1

The neurokinin (substance P) receptor (NK1R), also known as the tachykinin receptor 1, is another gene closely linked to dopaminergic activity in the prefrontal cortex (TACR1). Hyperactivity was discovered in a knockout mouse lacking the TACR1 gene (NK1R). Psychostimulants like D-amphetamine and methylphenidate were used to avoid hyperactivity of the individuals. The NK1R mice's behavioral and neurochemical abnormalities, as well as their aberrant

response to psychostimulants, are strikingly like the clinical features of ADHD in people. Four TACR1 SNPs (Single nucleotide polymorphisms) previously linked to bipolar illness and drinking were revealed to be a risk factor for ADHD in a study of 450 ADHD cases (34).

4 EPIGENETIC OVERVIEW ON ADHD

Prenatal and postnatal stress may have an impact on brain development, particularly in terms of emotional, motor, and cognitive elements or domains. Understanding the epigenome, or the epigenetic aspect of the organism is sometimes required to find the link between the phenotype and the genotype. This is likely because an organism's epigenetic state encompasses a wide variety of complicated and changeable molecular interactions. These occurrences are mostly utilized to determine the relationship between genotype and phenotype (4). According to the studies of Gustafsson and Kallen, ADHD has substantial connections with a variety of environmental factors (35). Some of those connections include parental ones, for example, their influence due to alcohol or drug intake. According to Wallis et al, some notions must be examined when it comes to the genetics of ADHD, which include:

i) A convincing argument for the involvement of a large genetic component.

ii) Complications that are involved.

iii) Proof that there are just a few genes that have a significant impact

iv) Candidate genes that have been discovered/identified

v) Participation in gene-environment interactions and interpretations (necessary basis of epigenetics) (36).

Epigenetic factors tend to open up a plethora of possibilities for disease susceptibility across the spectrum of neuropsychiatric disorders, including ADHD (37; 38; 39). Early exposure to high-stress, high-trauma situations has also been linked to the development of ADHD (40; 41; 42). Inadequate social and environmental situations can sometimes manifest themselves early in life by affecting cellular patterns of neurodevelopment, which subsequently can lead to the development of ADHD (43). In addition to being epigenetic factors, dopamine and serotonin are also associated with ADHD symptoms, particularly impulsive behavior (44). Another factor that can raise the likelihood of unfavorable neurobehavioral developmental outcomes and an ADHD risk factor is an adverse parenting environment, which affects around 10% of all US infants. (45; 46). Failure of executive inhibitory functioning is linked to emotional vulnerability and dysfunctional motor control which could also manifest in impulsive aggression, (47; 48; 49; 50; 51) which is frequently observed in ADHD people's maladaptive responses and inappropriate action (52; 53; 54). The epigenetic aspect of ADHD involves a variety of complicated genotyped entities, environmental realities, and endophenotypes that interact to express the gene and the symptom profiles associated with the disorder's pathophysiology. The epigenetic aspects of ADHD are also influenced by the therapeutic intervention (methylphenidate). According to several studies, some environmental pollutants such as lead, and polychlorinated biphenyls are a risk factor for the development of ADHD (4). Violent behavior (impulsive aggressiveness) and alterations in serotonin neurotransmission may be closely

related to impulsive conduct, which is described as "action without foresight" (4), when someone has been diagnosed with ADHD (55).

5 DIFFERENCE BETWEEN MEN AND WOMEN: A BRIEF ELABORATION

Studies indicate men are seemingly more likely to be diagnosed with ADHD than women (56). However, some studies have also shown that women are frequently misidentified and underdiagnosed (57; 58; 59; 60). This could be related to the fact that men and women express the disorder differently. The causes of these differences mostly remain unknown.

5.1 ADHD IN MEN

Symptoms of ADHD in men or boys indicate a higher likelihood of behavioral issues. It has been discovered that men and young boys with ADHD have more externalized issues (57; 58; 59) which are characterized by disruptive habits and mildly consistent non-compliance.

5.2 ADHD IN WOMEN

Women are more likely to have concurrent symptoms, which might be frequently undiagnosed (61). Women and young girls with ADHD have been observed to have more internalized disorders (57; 58; 59) which are characterized by emotional or psychopathological features and symptoms. Internalized symptoms are more difficult to notice, therefore increasing the chances of misdiagnosis (62).

5.3 COMPARISON OF ADHD IN MEN AND WOMEN

The ability to organize one's goals, keep track of them, and accomplish them successfully is known as having an executive function. Some of the "executive functions" include inhibition, problem-solving, working memory, and attentional control. Based on previous research, the effect on executive functions was identified as the primary symptom of ADHD (63; 64; 65; 66), which led to the discovery of some additional similarities between men and women with ADHD (67; 68). However, even though the effect on executive function is the primary symptom of ADHD, research is still underway to determine whether women with ADHD have a distinct neuropsychological profile when compared to their male counterparts (56). One of the most noticeable differences between men and women, or young boys and girls with ADHD, was that for the male counterparts, cognitive flexibility and verbal fluency were the qualities that were more evident, whereas for the female counterparts, working memory and inhibition were the qualities that were prominent (69).

6 THERAPEUTICS

Treatment for ADHD can be through medication, therapy, or other options **(Table 2).**

TABLE 2
Treatment modalities of ADHD

Category of treatment	**Types/Subtypes**	**Additional information**	
Medication	1. Stimulants 2. non-stimulants	1. Stimulants are the most prescribed type of medication. These increase the levels of dopamine and norepinephrine, resulting in a decrease in hyperactivity and improving the ability to concentrate. Examples: Adderall, Dexedrine, Focalin, etc. Side effects include increased blood pressure, hallucinations, etc. 2. Non-stimulants are used when the stimulants aren't as effective as planned. These contribute to improving attention and memory. Examples: Pamelor, atomoxetine, alpha-2-adrenergic agonists, etc. Side effects include seizures and suicidal thoughts. 3. Common side effects for both include headache, nausea, dry mouth, irritability, etc.	(70) (71)
Therapy	1. Behavior therapy 2. Cognitive behavioral therapy 3. Psychotherapy	1. In behavior therapy, the actions and habits are tracked, and treatment plans and techniques are prepared accordingly. For example, a reward system to encourage good behavior. 2. Cognitive behavioral therapy is a short-term therapy. It focuses on changing undesirable behavior according to the perspective of the patient on how they feel about the symptoms. This type of therapy is preferred if the individual struggles with procrastination, time management, irritability, or productivity. 3. This type of therapy focuses on the management of the symptoms by understanding them. Behavioral patterns can be understood, thereby helping the patient make better decisions in the future.	(72) (73) (74)

7 CONCLUSION

Various factors affect the development of ADHD. These factors could be classified as genetic and manifested through inheritance, mutations, epigenetic factors, gene-by-gene/gene-by-environment interactions, certain chromosomal disorders, as well as non-genetic causes manifested by certain environmental factors like social factors, prenatal and postnatal stress, biohazards, or occasionally through neurological contributions. Furthermore, there are significant differences between men or young boys and women or young girls with ADHD. The knowledge of the myriad of factors that influence ADHD could be vital in designing efficient and effective therapeutics against this disease. In addition, the difference in symptoms between men and women could also be exploited to understand the development of ADHD for improved and personalized remedies. However, as ADHD is a heterogeneous and a multifactorial disorder, a lot of additional research is required to have a complete understanding of the disorder to aid in the development of effective therapeutics.

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