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# The Predictive Power of Attention-Deficit Hyperactivity Disorder (ADHD) Genetic Risk Factors

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## Abstract

*Issues regarding disorganization and hyperactivity are large burdens on the pediatric population, and the severity of these behavioral disorders, called attention-deficit hyperactivity disorder (ADHD), falls on the slow-developing treatments that are unable to fully solve the symptoms of those affected. Limiting factors include the heterogeneous responses that many patients have in response to pharmacological treatments, the range of comorbid symptoms and conditions associated with ADHD, and the intricacies of the environmental and genetic interactions involved. Since ADHD has a strong genetic component with up to 80% heritability for the condition, epigenetic and genetic studies offer valuable insight into how future treatments could tackle the issue. In particular, the studies reveal how genes might provide indicators for patients' response to medication, their symptomatology, and unique risks for comorbidities. This paper outlines the current pharmacological and cognitive treatments for ADHD, discusses their limitations, and offers an overview of present genetic risk factors to analyze how they may provide insights for detection, prevention, and responses to treatment.*

## Introduction

### 1.1 Introduction to ADHD

Attention-deficit hyperactivity disorder (ADHD) primarily affects children and adolescents. As of 2016, there are 6.1 million (9.4%) children aged 2-17 diagnosed with ADHD in the United States<sup>1</sup>. Along with that, 1 in 20 children in the United States are being medicated for ADHD<sup>1</sup>. While present in younger populations, it can persist into adulthood as well. 2.5-4.4% of adults in the United States are diagnosed with ADHD and around 2.8% of adults worldwide<sup>2</sup>. The main characteristic behaviors defined by this disorder can include hyperactivity, short attention span, and impulsiveness. Children and adults can display these symptoms differently. Hyperactivity and impulsiveness tend to be traits shown more in children while inattentiveness is more persistent in adults<sup>3</sup>. For example, children can exhibit hyperactivity by not being able to sit still. Adults on the other hand can show signs of inattention by not being able to sit through long activities or interrupting people's sentences while they talk.

### 1.2 Causes of ADHD

The causes and the risk factors of ADHD are unknown to this day. However, it is believed that genetics plays a very important role in the development of ADHD in individuals<sup>4</sup>. ADHD tends to run in the family, transmitted through genes inherited from one's parents<sup>5</sup>. Recent analysis of twin studies demonstrates 80% heritability for the condition, though no specific genes have been linked to ADHD<sup>6</sup>. Along with genetics, some risk factors include brain injury, exposure to environmental risks during pregnancy or at a young age, alcohol or tobacco use during pregnancy, premature delivery, or low birth weight<sup>4</sup>.

### 1.3 Diagnosis of ADHD

Currently, there are no convenient or definitive ways to diagnose ADHD. Children can get diagnosed with ADHD by a pediatrician, adult psychiatrist, or qualified healthcare professional with training in ADHD<sup>7</sup>. A physical examination is run to make sure the symptoms relayed are not caused by something other than ADHD. Then, an interview can be

conducted with the child and parent. To be diagnosed with ADHD, multiple symptoms must be displayed. Additionally, the patient must experience these symptoms for over six months and before the age of twelve<sup>7</sup>. This process can be different for adults, though specialists will ask the adult about symptoms that they have. However, an adult will not get a confirmed diagnosis unless they affirm that symptoms were present in childhood<sup>7</sup>. All of these diagnostic tests mainly involve speaking to a specialist or doctor because no blood or invasive tests can diagnose ADHD<sup>8</sup>.

#### **1.4 Current Treatments**

The most popular treatments of ADHD include the use of medical stimulants or non-stimulants. Medical stimulants aim to correct biochemical imbalances by increasing dopamine and norepinephrine levels to increase attention and focus<sup>9</sup>. Stimulants target the brain's reward system, the mesolimbic dopamine pathway involving the ventral tegmental area of the midbrain, medial prefrontal cortex, and limbic system<sup>10</sup>. In general, stimulant medications have three functions. It could mimic neurotransmitters such as dopamine to increase stimulation of dopamine receptors. It could increase the time in which dopamine stays within the receptors by preventing its degradation. This could occur through blocking reabsorption or enzymatic degradation<sup>10</sup>. The FDA was able to approve 29 medical stimulants including Adderall, Dexedrine, and Ritalin, and all twenty-nine of these stimulants have something in common: the use of either the molecule amphetamine or methylphenidate<sup>9</sup>. This is a popular choice of medication for ADHD because it is proven to help around 70-80% of children with the diagnosis<sup>9</sup>.

Although stimulants provide good results for most pediatric patients, there are some downsides of using them. The side effects of these stimulants include an increased heart rate, increased blood pressure, decreased appetite, anxiety, and a chance of addiction to medications<sup>9</sup>. Along with that, stimulants are not a good long-term treatment for ADHD. The need for each dose of the stimulant increases over time and it was found that stimulants may have less efficacy over time<sup>9</sup>.

Since there are downsides to using stimulants, non-stimulant medications are a relatively new medical option that was created to reduce the likelihood

for drug misuse<sup>9</sup>. Non-stimulants and stimulants are very similar with the main difference being the target neurotransmitter. Strattera (Atomoxetine) was the first FDA approved non-stimulant medication for ADHD with Clonidine, Guanfacine, and Qelbree following not soon after<sup>9</sup>. Non-stimulants have fewer side effects, but side effects like nervousness, sleep problems, fatigue, upset stomach, dizziness, or a dry mouth can still happen<sup>9</sup>. Although it seems like non-stimulants are a good option of treatment, it can be less reliable as 20-30% of people with ADHD have stated that it does not work for them<sup>9</sup>.

Another option for treatment for ADHD is cognitive behavioral therapy, also known as CBT. CBT is a short-term psychotherapy that focuses on changing a person's negative perspective of themselves<sup>11</sup>. This could mean changing the way one thinks about themselves and their potential. The way CBT works is that each session identifies situations where a lack of organization creates problems in a person's everyday life<sup>11</sup>. Therefore, these sessions help the person develop coping skills to deal with challenges and obligations. These sessions can also include time for relaxation and meditation as well. There is a recent study that shows the positive effect of CBT through a randomized controlled trial<sup>12</sup>. The study primarily focused on determining how a treatment called Accessing Campus Connections and Empowering Student Success (ACCESS), a CBT program, affects 250 college students with ADHD over a course of two semesters. The study assessed primary characteristics associated with ADHD such as executive functioning, depression, and anxiety. The results of the study show that CBT reduced these common ADHD symptoms. Furthermore, a learning curve growth of students was modeled and it showed improvements compared to groups not in the ACCESS participants. There were no ascertained changes seen in depression and anxiety with correlations for lower chances in worsening depression and anxiety symptoms. Therefore, it provides concrete evidence for ACCESS being used as treatment for college students with ADHD<sup>12</sup>.

## Genes of Interest

As discussed earlier, genes play a primary role in the cause of ADHD. Currently, no studies have identified a specific gene that causes ADHD. Part of the difficulty lies in the complexity of the phenotypes and relatively small effects of genetic variants<sup>13</sup>. This section will lay out and discuss the different genes of interest that could possibly relate to the cause of ADHD.

Gene of Interest	Function in the Body	Relation to ADHD
Neurexin 1 (NRXN1)	Bind proteins → Neurotransmitter release and differentiation of synapse	Mutations in gene → learning or memory problems → ADHD
Dopamine Receptor D3 (DRD3)	Controls cognition, impulse control, attention, and sleep	Mutations in gene → cognition and impulsiveness problems → ADHD
Glutamic Acid Decarboxylase 65 (GAD65)	Catalyzes the conversion of glutamic acid into inhibitory neurotransmitter $\gamma$ -amino butyric acid (GABA) → neurotransmission	Serum of anti-GAD65 antibodies in patient → ADHD
Patched Domain Containing 1 gene (Ptchd1)	Provides thalamic reticular nucleus activity	Deletion of gene reduces thalamic reticular nucleus activity → attention deficits and hyperactivity → ADHD
Norepinephrine Transporter (SLC6A2)	Primary destruction mechanism of noradrenaline (NE) and involved in the reuptake of dopamine (DA) and NE into the presynaptic neuron	Effects treatment of ADHD (use of non-stimulants) v

**Figure 1:** This table summarizes the five genes of interest, their functions in the body, and its relation to ADHD.

### 5.1 Gene of Interest 1: Neurexin 1 (NRXN1)

The first gene of interest is a family of cell adhesion proteins called neurexins. Neurexins are encoded mainly by NRXN1, NRXN2, and NRXN3 genes among others<sup>14</sup>. The main role of neurexins in the cell surface of the neurons is to bind to other proteins and alpha-latrotoxin presynaptic receptors. The binding of these proteins can in return lead to

neurotransmitter release and differentiation of synapse<sup>15</sup>. However, the failure to bind together and the miscommunication of the bindings between these proteins is linked to a specific neurexin: NRXN1<sup>14</sup>. Along with playing an important role in protein binding, another crucial role of NRXN1 is helping many proteins in synaptic transmission. The failure of NRXN1 to carry out these functions within the cell may be a reason for the development of learning or memory, which is a sign of ADHD in a patient<sup>15</sup>.

There are some in vivo studies that have correlated NRXN1 with ADHD. For instance, researchers conducted one study to evaluate the protective effect and potential mechanism of NRXN1 on learning and memory in ADHD rats<sup>15</sup>. The methods involved grouping the four-week-old rats into two categories: spontaneously hypertensive rats (SHRs) and normal Sprague Dawley (SD) rats. These groups of rats were tested by using a Morris water maze on a learning and memory test. Moreover, qPCR and western blots were used to analyze the expression levels of NRXN1 at mRNA and protein levels. It was concluded that the overexpression and interference of NRXN1 played a role in impairing the ability of the rats to learn and memorize things in both the SHRs and SD rats<sup>15</sup>. However, in the experiment, a portion of the SD rats were given treatments with methylphenidate (MPH) during the trails. This was shown to make an improvement in the performance of the treated SD rats. The change in NRXN1 in the rats led to a change in other synapse-related genes including PSD95, SYN1, GAP43, and NLGN1 genes. Therefore, it can be concluded that NRXN1 deficiency is associated with the expression of synapse-related genes and ADHD pathogenesis and can be a potential therapeutic target for ADHD treatment<sup>15</sup>.

## **5.2 Gene of Interest 2: Dopamine receptor 3 (DRD3)**

Another gene of interest is in the dopamine receptor family, which encodes dopamine receptors D1, D2, D3, D4, and D5<sup>16</sup>. Dopamine receptors as a family are used in everyday function. It affects the brain as it is able to control and process emotions and movement of the body<sup>17</sup>. In particular, dopamine receptor D3 (DRD3) affects your cognition, impulse control, attention, and sleep<sup>17</sup>. The mutation of DRD3 mainly leads to different

diseases such as Schizophrenia and Tremor. These mutations can be caused by Ser-9-Gly, a nucleotide polymorphism in DRD318. Ser-9-Gly has a C allele in it which encodes glycine and a T allele which encodes serine<sup>13</sup>.

There are quite a few in vitro studies that have tried to correlate DRD3 mutations with ADHD, but not a lot of them have been successful<sup>18</sup>. However, there is a DRD3 gene and ADHD pharmco-behavioral genetic study that links the two together<sup>13</sup>. The main goal of the study was to examine multiple types of potential genes related to ADHD. This was done using an exploratory analysis with a comprehensive approach. 575 children with ADHD aged 6 to 12 were the subjects of the study and were assessed under three of the experimental conditions. The conditions include one week of baseline observation, one week of methylphenidate (MPH), and one week of placebo<sup>18</sup>. Their parents, teachers, and research staff evaluated their quantitative behavioral and cognitive dimensions relevant for ADHD. The results of the experiment showed a nominal association between the T allele and worse behavioral scores while the subjects were in the MPH week. Along with that, the T allele demonstrated a nominal association with increased risk for ADHD, response to placebo and MPH<sup>13</sup>. The conclusions that could be drawn from this are that DRD3, and moreover Ser-9-Gly, play a role in the cause of ADHD and variations in patient's behavior<sup>18</sup>.

### **5.3 Gene of Interest 3: Glutamic Acid Decarboxylase 65 (GAD65)**

Glutamic Acid Decarboxylase 65 (GAD65) is another gene to investigate as it has been found in the serum of patients with several neurological disorders. GAD65 is an enzyme that is produced primarily by pancreatic islet cells<sup>19</sup>. The primary role of GAD65 is that it catalyzes the conversion of glutamic acid into inhibitory neurotransmitter  $\gamma$ -amino butyric acid (GABA) that is present in synaptic vesicles of GABAergic neurons for its release during inhibitory neurotransmission<sup>20</sup>.

Serum anti-GAD65 antibodies can be a common marker of subgroups of patients with autism and ADHD as shown in a study that correlated the presence of GAD65 antibodies in the serum of children with autism or ADHD<sup>20</sup>. In the study, there were 14 normal control patients, 20 patients with autism, and 15 patients with ADHD. The GAD65 antibodies and

total IgG were assessed in the serum of normal patients and patients diagnosed with either autism or ADHD<sup>20</sup>. In conclusion, none of the normal patients had GAD65 in the serum, 15% of children with autism had GAD65 detected, and 27% of children with ADHD had GAD65 in their serum. With this, 60% of autistic and 53% of ADHD patients reacted with Purkinje neurons in mouse cerebellum and 20% of ADHD patients' serums reacted with the cells in the molecular and granule cell layers and the cells in the vicinity of the Purkinje neurons<sup>20</sup>. Therefore, it can be concluded that the serum anti-GAD65 antibodies are associated with patients with autism and ADHD.

#### **5.4 Gene of Interest 4: Patched Domain Containing 1 gene (Ptchd1)**

The Patched Domain Containing 1 gene (Ptchd1) is another gene of interest as many studies and models have displayed this gene's role in ADHD. Its deletion reduces the thalamic reticular nucleus activity, a region of the brain that synapses the entire cortex and cerebellum. Knockouts of this gene led to symptoms of attention deficits and hyperactivity due to its involvement with small conductance calcium-dependent potassium currents (SKs) within the thalamic reticular nucleus<sup>21</sup>.

In one of these experiments, acute injection of the SK positive allosteric modulator 1-ethyl-benzimidazolinone EBIO rescued the ADHD-like knockout behaviors<sup>21</sup>. By measuring the mouse's thalamic activity with a fluorescence resonance energy transfer, the sensory-related functions of mice were found to be lower in knockouts but recovered with the injection. This suggests that SK channel dysfunction can be a target without effects on aggression, hypotonia, and learning deficits. It targets only inattention. In another study, Ptchd1 KO mice showed drastic changes in kynurenine pathway metabolite concentrations in the serum and the brain, indicating that the activated KP is associated with ADHD-like behaviors. This pathway is implicated in generating cellular energy in the form of nicotinamide adenine dinucleotide (NAD<sup>+</sup>). Because energy requirements are substantially increased during an immune response, the KP is a key regulator of the immune system. Having the Ptchd1 gene have a close tie to the KP pathway indicates the association between ADHD and the



anti-inflammatory responses of the immune system. Global PTCHD1 knockout mice were used to measure neuronal, behavioral, and social function with respect to a gene associated with ADHD and ASD-like symptomatology. Markers of symptomatology can be determined through KP impairments. Thus, there is potential for KP to be used as a clinical biomarker when the PTCHD1 gene is inactivated<sup>21</sup>.

### **5.5 Gene of Interest 5: Norepinephrine Transporter (NET)**

Atomoxetine (ATX) is the most commonly used drug in a non-stimulant group in the ADHD treatment. It acts by increasing the levels of dopamine (DA) and norepinephrine (NE) by inhibition of presynaptic NET in the prefrontal cortex<sup>9</sup>. The Norepinephrine Transporter (SLC6A2), which is responsible for the primary destruction mechanism of NE, is found in the plasma membrane of noradrenergic neurons involved in the reuptake of DA and NE into the presynaptic neuron. The function of the NE transporter is attributed to multiple allelic variations of the SLC6A2 gene.

In a recent study, heterozygous genotypes rs12708954 genotypes showed greater side effects during treatment than normal genotypes. Similarly, in rs3785143 genotypes, side effects in heterozygous carriers have been reported more frequently than WT carriers. In only one pilot study, rs3785143 T allele carriers reported a loss of appetite and irritability during ATX treatment<sup>22</sup>. This gene polymorphism implies that ADHD genetic risk factors not only influence its symptomatology, but also modulate the effectiveness of stimulant treatment such as ATX on the patient's response.

### **Future Investigations**

ADHD is a heritable condition, although the inheritance, or rather the likelihood of the disease being passed onto the next generation, is complex. While ADHD genetic components are supported by twin studies and slightly less so by GWAS studies, genetic studies provide a close estimate to how multiple factors could intertwine and lead to comorbidities. The late-onset form of ADHD has not been studied enough. Therefore,

conflicting results on genetic studies provide little information about the late-onset of ADHD in adults compared to children.

Understanding heritability, long-term causes, and environment-gene interactions are required in whole-genome sequencing analyses. As of current literature, genetic studies of ADHD have been targeted to risk factors. By identifying these genetic underpinnings, it could reveal whether or not people with certain genes have resilience towards ADHD given an environmental condition. Understanding this interrelationship between genetic resilience and the genetic risk factors is important going forward.

## Conclusion

Research on ADHD and ways to treat it have been researched widely in the past several years. Current treatments mainly include the use of stimulants or non-stimulants as medication. Also, cognitive behavioral therapy (CBT) is another popular way to help patients deal with ADHD. Along with this, there is new research that provides evidence that ADHD is inheritable and can run in families. With this new information, it can lead to the belief that focusing on gene mutations for treatment is a good next step to finding a new treatment for ADHD. There have been multiple genes that have been discussed including Neurexins 1 (NRXN1), Dopamine receptor D3 (DRD3), Glutamic Acid Decarboxylase 65 (GAD65), Patched Domain Containing 1 gene (Ptchd1), and Norepinephrine Transporter (SLC6A2). Multiple in vivo studies have demonstrated the link between these genes and ADHD. While all of this is known, there is still a lot to learn in this area. There is a lack of clinical trials and testing which is essential to determine whether or not these genes can be successfully mutated and provide significant improvements to patients with ADHD.

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