

Spring 2018

# The Genetics of ADHD: A review of polymorphisms in neurotransmitter system genes

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## Recommended Citation

Spahija, Ada, "The Genetics of ADHD: A review of polymorphisms in neurotransmitter system genes" (2018). *Olin Prize for Undergraduate Library Research*. 1.

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The Genetics of ADHD: A review of polymorphisms in neurotransmitter system genes

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BIO 308

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7 December 2017

### *ADHD: Overview and Heritability*

Attention deficit hyperactivity disorder (ADHD) is a mental disorder that is primarily categorized by lack of sustained attention, impulsive behavior, and hyperactivity (Barkley, 1997). These symptoms are usually first presented in early childhood and do not diminish overtime, but rather continue into adulthood in 50-80% of cases. Individuals with ADHD are often at risk of lower achievement in school due to their short attention span and hyperactivity, as well as behavioral and social problems due to their impulsive tendencies (Barkley, 1997). When ADHD was first discovered in the early 1900s, its symptoms were thought to be a result of lack of motivation and irregular behavior due to skewed morality (Still, 1902). Over a decade later it has become very clear that, while there may be environmental risks associated with the acquisition of ADHD, the disorder can be mostly explained by molecular biology and genetics (Faraone et al., 2005). To confirm the heritability of ADHD, many case studies have been done to look for a familial linkage. By controlling for environmental factors such as family make-up and socioeconomic status, it has been shown that children with parents who have ADHD are two to eight times more likely to also have the disorder, simply due to genetics (Faraone et al., 2005). This genetic factor was further confirmed by studying twins to see if identical twins, who share identical DNA, are more likely to jointly inherit ADHD than fraternal twins, who only share half of their DNA. By comparing the heritability among 20 studies of twins in the United States, it was confirmed that the average heritability of ADHD is 76%, making it one of the most heritable psychiatric disorders in existence (Coolidge et al., 2000).

While ADHD can be clearly established as a genetic disorder, the exact mechanistic causes have not been confirmed, though a multitude of studies have been and are being

done to identify specific genes and their effects on the development of the disorder. Biologically relevant genes, those whose physiological roles would theoretically influence ADHD development, have been studied in affected patients and control subjects. Allele frequencies are used to determine alleles that are more commonly present in ADHD patients, indicating a possible genetic risk for the disorder (Barkley, 1997). Also, mutations in relevant genes that are present in ADHD patients can be a likely cause of the disorder if subjects with the wild-type gene are mostly unaffected. Genes involved in neurotransmitter pathways, such as dopamine and serotonin systems, have been heavily studied and are the current strongest candidates for a molecular basis for ADHD.

This review will discuss polymorphisms in genes that are involved in different neurological systems associated with ADHD. The most established and first-studied system is the dopaminergic system, which is responsible for the mobilization and re-uptake of dopamine, a neurotransmitter that contributes to the brain's reward system (Thapar et al., 2005). The next system, the serotonergic system, is mechanistically similar to its dopaminergic counterpart, but involves the neurotransmitter serotonin, which contributes to aggression and impulse control (Virkkunen et al., 1995). Finally, the noradrenergic system will be discussed, due to its role in norepinephrine release, which is associated with cognitive and nervous system functions (Arnsten et al., 1996).

### **Polymorphisms in Dopaminergic Genes**

The dopaminergic neurotransmitter system has been the most extensively studied in relation to ADHD, due to neurological and pharmacological evidence confirming its involvement in the disorder (Thapar et al., 2005). This involvement is most clearly seen in the high response rate of ADHD to stimulant medications that increase the availability of

dopamine, such as methylphenidate, which inhibits the dopamine transporter DAT1 (Cortese and Castellanos, 2012). DAT1, encoded by the gene SLC6A3, is involved in reuptake of dopamine from the synaptic cleft, diminishing its effects in the brain by reducing its availability to bind and activate receptors (Šerý et al., 2015). Because of the success of dopamine-enhancing drugs in relieving symptoms of ADHD, it is reasonable to believe that the dopaminergic system has a critical role in the disease mechanism and mutations in genes encoding for proteins in this system may cause ADHD.

The first candidate gene studied in the dopaminergic system was DAT1. Some patients with ADHD have a high risk of a 10-repeat allele in the SLC6A3 gene, causing excess copies of the DAT1 protein (Heinz et al., 2000). Extra copies of a dopamine reuptake protein would theoretically cause a lack of dopamine availability in an individual, contributing to an ADHD phenotype via decreased dopaminergic functions. However, the finding of altered DAT1 levels in diseased patients has not been consistently reproduced, so it is difficult to confirm that this is a true genetic cause of ADHD. In a study by Swanson et al. (2000), the high-risk DAT1 allele actually occurred more often in control subjects than in ADHD patients. This may have been due to a small sample size producing skewed results, but it is still important to explore other dopaminergic genes in order to establish a relation between the neurotransmitter system and ADHD.

Another gene that has been extensively studied in relation to ADHD is the dopamine D4 receptor gene (DRD4). When activated by dopamine, this receptor is involved in attention, motivation, and reward mechanisms (Robbins and Everitt, 1996). An allele for DRD4 containing seven repeats in the third exon has been associated with ADHD as well as externalized aggressive behavior in children (Bakermans-Kranenburg et al., 2008). This is

because the 7-repeat allele has a decreased affinity for dopamine, due to a mutation in the DRD4 protein that results in a conformational change in a cytoplasmic loop of the receptor (Tovo-Rodrigues et al., 2013). While the exact mechanism for neuro-functional problems in ADHD patients with mutated DRD4 is not completely understood, it is possible that the protein is important in motivational processes in the brain, due to its prevalence in the prefrontal cortex (Primus et al., 1997). A study by Shaw et al. (2007) showed that the 7-repeat allele for DRD4 is associated with decreased cortical thickness in the frontal lobe of the brain, which may be a cause of the neurological symptoms of ADHD. This hypothesis correlates with the “motivational pathway” that ADHD symptoms can take, which occurs when the reward mechanisms of the brain (located in the frontal cortex) are not functional, resulting in behavior problems, impulsiveness, and difficulty engaging in tasks (Toplak et al., 2005).

### **Polymorphisms in Serotonergic Genes**

While the dopaminergic neurotransmitter system clearly contains susceptible genes for ADHD development, studies have shown that serotonin neurotransmission also has an important role in the genetics of this disorder. Lack of serotonin impacts many mental processes such as anxiety and depression and has been associated with lack of impulse control (Virkkunen et al., 1995). Serotonin levels are typically low in blood platelets of ADHD patients and their cerebrospinal fluid contains higher levels of 5-hydroxyindoleacetic acid, a metabolite of serotonin synthesis (Ribasé et al., 2009). Also, mice models for ADHD have shown decreased hyperactivity when given serotonin agonists and serotonin reuptake inhibitors, which both increase the amount of serotonin or serotonin-like molecules in the body (Gainetdinov et al., 1999).

There are fourteen receptors involved in serotonin recognition with serotonin receptor 1B (5-HT1B) present in most mammals, including humans (Bouwknicht et al., 2001). In humans, polymorphisms of this receptor are associated with antisocial behavior and addiction (Lappalainen et al., 1998). In addition, mice lacking 5-HT1B receptors, accomplished via gene knockout, were more hyperactive and aggressive than wild mice that had normal levels of the serotonin receptor (Bouwknicht et al., 2001). This association was further confirmed in humans by examining polymorphisms in the HTR1B gene, which encodes for the 5-HT1B receptor (Smoller et al., 2006). The G861C variant of the gene and a polymorphism in the 3' UTR of HTR1B (A1180G) are associated with ADHD, possibly due to a mutated receptor in the G861 variant and decreased mRNA stability via poly-A tail damage in the A1180G variant (Smoller et al., 2006).

The serotonin receptor 2A gene (5HT2A) may also be involved in ADHD, with a SNP in exon three of the gene leading to combined ADHD subtypes in a study of 451 adult and children patients (Ribasé S et al., 2009). Notably, the receptor encoded by 5HT2A is also utilized in dopamine neurotransmission by inhibiting dopamine release, a known cause of hyperactivity (O'Neill et al., 1999). This shows that the serotonergic system make contribute to ADHD through its involvement in the dopaminergic system, rather than the two pathways acting independently. This interaction was tested in DAT knockout mice, which were lacking a dopamine receptor. Exogenous 5HT2A receptor agonists were added to the mice and they showed reduced signs of hyperactivity, indicating that inhibition of the serotonergic receptor led to increased dopamine availability, even when dopamine receptors were lacking (Gainetdinov et al., 1999). Further studies are required to confirm mechanisms that may cause ADHD based on interactions between dopamine and serotonin

pathways, but it is clear that some type of connection exists between the relatedness of these pathways and hyperactivity.

### **Polymorphisms in Adrenergic Genes**

The noradrenergic system is responsible for mobilizing the neurotransmitter/hormone norepinephrine in response to stress, enhancing focus and stimulating the nervous system of an individual to increase alertness (Arnsten and Li, 2005). In the absence of stress, norepinephrine in the prefrontal cortex of the brain serves to enhance cognitive function by activating adrenergic receptors that are associated with noradrenergic terminals (Arnsten et al., 1996). Norepinephrine receptors and transporters have been extensively studied in relation to ADHD and polymorphisms in genes encoding for these receptors may make individuals more susceptible to the disorder.

The alpha-2A adrenergic receptor (ADRA2A) has been examined in case studies of ADHD patients and a SNP at nucleotide 1291 in the gene (C to G) has been associated with ADHD symptoms in patients with Tourette's syndrome (Comings et al., 2003). Similarly, a family-based study in ADHD patients showed a significant correlation between the ADRA2A allele with guanine at position 1291 and lack of sustained attention (Roman et al., 2003). However, a similar association between a polymorphism in the alpha-2C adrenergic receptor (ADRA2C) and ADHD was not significant after statistical analysis, a finding that has been replicated in family studies (Barr et al., 2001). Because of the lack of solid evidence to suggest that mutations in adrenergic receptors cause ADHD-risk, it is important to study other aspects of the noradrenergic system.

The norepinephrine transporter, encoded by the SLC6A2 gene, has also been analyzed in ADHD patients, mainly due its pharmacological significance. Drugs that block

this transporter are highly effective in the treatment of behavioral ADHD symptoms such as hyperactivity and lack of sustained attention (Biederman and Spencer, 2000). In the Comings et al. (2003) study of patients with Tourette's syndrome, there was an association between a polymorphism in SLC6A2 and ADHD symptoms. However, in a study examining 122 families with genetic ADHD, there was no evidence to suggest that polymorphisms in SLC6A2 were disease-causing (Barr et al., 2002).

While polymorphisms in noradrenergic system genes have not been conclusively linked to ADHD, there is clearly some type of connection between this neurotransmitter system and disordered phenotypes. This may be a result of the interconnected effects of the norepinephrine and dopamine pathways. For example, norepinephrine acts as a dopamine agonist on the dopamine D4 receptor (Lanau et al., 2002). This could explain the reason why inhibiting the norepinephrine transporter is effective in treating ADHD, even though there is no clear evidence that norepinephrine receptors are involved in the disorder. The increased availability of norepinephrine as a result of blocking re-uptake transporters may allow the molecule to bind and activate DRD4, rather than just ADRA2A, relieving ADHD symptoms by activating the dopaminergic system. More research is needed to confirm this hypothesis or any clear involvement of the noradrenergic system in ADHD.

### **Conclusion: Neurotransmitter involvement in ADHD**

Attention deficit hyperactivity disorder is a neurological disorder with many possible causes, including mutations in genes that are involved in neurotransmitter pathways. The dopaminergic system, responsible for utilizing dopamine, is essential in reward-motivated behavior. Lack of this molecule potentially causes impulsive behavior and difficulty focusing on tasks, two symptoms of ADHD. Polymorphisms in dopamine

receptor and transporter genes have been studied, with DAT1 and DRD4 showing the highest likelihood of being linked to ADHD. The serotonergic system mobilizes serotonin, which aids in impulse control and keeps anxiety at bay. Without adequate levels of this neurotransmitter, ADHD-associated hyperactivity can occur in an individual.

Polymorphisms in the serotonin receptors 5-HT1B and 5HT2A have been shown to be associated with ADHD. Finally, the noradrenergic system is responsible for the release of norepinephrine, a hormone that can act as a neurotransmitter in the brain to aid in cognitive function and focus. While no clear evidence has been found to establish this system's involvement in ADHD, the norepinephrine receptor ADRA2A and transporter SLC6A2 have been shown in some cases to be mutated in ADHD patients. A more likely explanation of this system's involvement in the disorder is through its relationship to the dopaminergic system, which has already been established as a factor in ADHD.

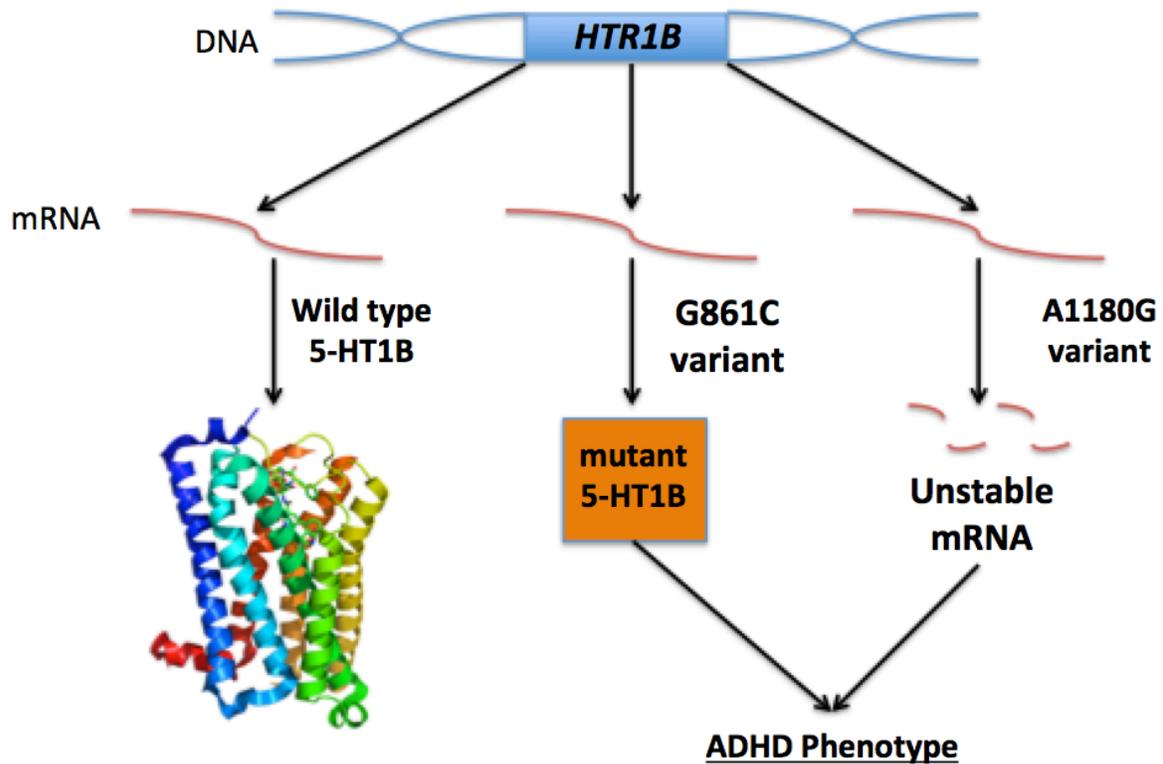
### **Future Directions: Novel Gene Studies and ADHD Treatments**

Future candidate gene studies are needed to provide statistically significant results that detect a true association between neurotransmitter system genes and ADHD.

Increasing the sample size of case and family studies, as well as exploring novel genes that may be more directly related to the disorder phenotype, may provide more cohesive results. Genome-wide association studies (GWAS) between ADHD and another neurological disorder that shares similar phenotypes could be done to discover novel genes that are involved in ADHD, which could possibly have significant risk-causing alleles. A very recent GWAS between ADHD and obsessive compulsive disorder (OCD), which shares similar pathology to ADHD, showed limited genetic overlap, indicating that this method needs to be used more and be deemed successful to reliably find novel genes that are

involved in ADHD (Ritter et al., 2017). In addition, when studying a candidate gene, multiple polymorphisms should be examined rather than only one or a few specific mutations. While one or two conserved mutations may be highly present in a population of interest, this does not mean that they are necessarily most likely to cause ADHD. Finally, although correlations between genetic mutations and ADHD symptoms have been discovered, precise mechanisms for these associations need further research. Studying gene-to-gene as well as gene-to-environment interactions could provide more detailed explanations of why polymorphisms in certain genes lead to ADHD phenotypes.

Establishing genes that are involved in ADHD would provide knowledge that has clinical significance, allowing pharmacologists to know precisely what proteins to target with drugs and even what genes to target with gene therapy. This could reduce the use of stimulant drugs to treat ADHD, such as the popular amphetamine Adderall, which have potentially dangerous cardiac side effects due to their role in increasing heart rate and blood pressure (Sinha et al., 2016). Designing drugs that inhibit or activate specific proteins that are encoded by genes known to be involved in ADHD would result in more specific treatment plans and less adverse drug effects, potentially improving the quality of life of ADHD patients.



**Figure 1. Mutations in the DNA sequence of the HTR1B gene results in either mutant 5-HT1B protein or unstable mRNA transcript, both of which may cause ADHD.** *Left:* The HTR1B gene codes for wild type 5-HT1B serotonin transporter protein (PDB ID: 4IAR) when there are no mutations in the DNA. *Middle:* When HTR1B carries the G861C mutation, the resulting 5-HT1B protein is mutated, leading to ADHD symptoms. *Right:* When HTR1B has the A1180G mutation, the 5-HT1B protein is not made due to degradation of unstable mRNA, also leading to ADHD symptoms. Crystal structure of 5-HT1B obtained from Wang et al. (2013).

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