Understanding the Genetics of ADHD

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common childhood disorders. Recently, it has been a source of debate and criticism in the media due to the increase in diagnoses. Despite the controversies surrounding overdiagnosis, treatment, and the disorder itself, one clear thing is that there is a genetic component to ADHD. In understanding ADHD as a whole, the discussion must start with the history and symptoms of the disorder, then focus on heritability, searching for a causal gene, and finally, analyzing possible genes of interest.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) has been described for centuries and is now the most common childhood disorder, affecting around 10% of the US population. ADHD has three core symptoms, which include inattention, hyperactivity, and impulsiveness that generally disrupt functioning (Mahone, 2017). The impairment must also be present in multiple environments (Holland, 2019). This disorder was initially named hyperactive/hyperkinetic syndrome in the 1980s, and the use of stimulants as treatment led people to believe that the root cause was some sort of brain damage. Then, as research into this disorder continued, the name evolved to Attention Deficit Disorder (ADD). With the publication of the DSM-III, it was finally renamed ADHD, which included the inattentive, hyperactive/impulsive, and combined subtypes with the DSM-IV. The DSM-V diagnostic guidelines include the age of onset being 12 years of age, with symptoms of inattention and/or impulsivity/hyperactivity being present. It also added an addendum where those over 17 could be diagnosed if they had five symptoms of inattention and/or impulsivity/hyperactivity (Mahone, 2017). Like many mental disorders, the definition of ADHD has changed over time, adjusting for new knowledge and research.

Heritability of ADHD

Research involving twin studies has found that the heritability is between 70-80%, and if a person has a first-degree relative with ADHD, they will have 5-105-10 times the risk of also developing ADHD (Mahone, 2017). In their paper, Faraone and Larsson review the data on twin, family, and adoption studies, as well as discuss genome-wide association studies, when discussing the heritability of ADHD (Faraone, 2019). One of the studies Faraone and Larsson reviewed encompassed a study of 894 people with ADHD who had siblings between the ages of 5-17. This study found that their rate of ADHD was 9 times higher than in those who did not have siblings with ADHD (Faraone, 2019). Additionally, adoption studies suggest that genetic factors could be more impactful than environmental factors. Then, when working with twin studies, researchers take advantage of the differences between monozygotic and dizygotic twins (Faraone, 2019). Monozygotic twins are commonly called identical twins, and they share 100% of their genetic makeup. On the other hand, dizygotic twins only share 50% of their DNA and are no more related to each other than a non-twin sibling would be. Overall, studies with both types of twins are very important in determining the heritability of a gene/disorder. Specifically, monozygotic twins help to compare the effects of the environment on the development of a disorder. In these twin studies, they estimated that the mean heritability of ADHD was 74% (Faraone, 2019). Faraone conducted a meta-analysis that included a Swedish study composed of 16,366 twins that found a strong connection between the extreme and subthreshold criteria of ADHD. The findings of Faraone 2019

are significant to the discussion surrounding heritability due to the amount of data they compiled into their meta-analysis.

Faraone and team compiled data around the heritability of ADHD from many different studies in Figure 1 of their paper. These studies had publication years from 1971 to 2017. These comparisons are significant as they show that the heritability of ADHD has been in scientific discussion for the past 50 years. Additionally, this comparison shows that all mentioned studies, with one exception, had a heritability of 0.6 or greater, indicating the heritability of ADHD to be greater than 50% at a minimum. This measure means that the differences seen are due to genetic factors rather than other factors. Additionally, this comparison strengthens the argument that ADHD has a strong genetic component.

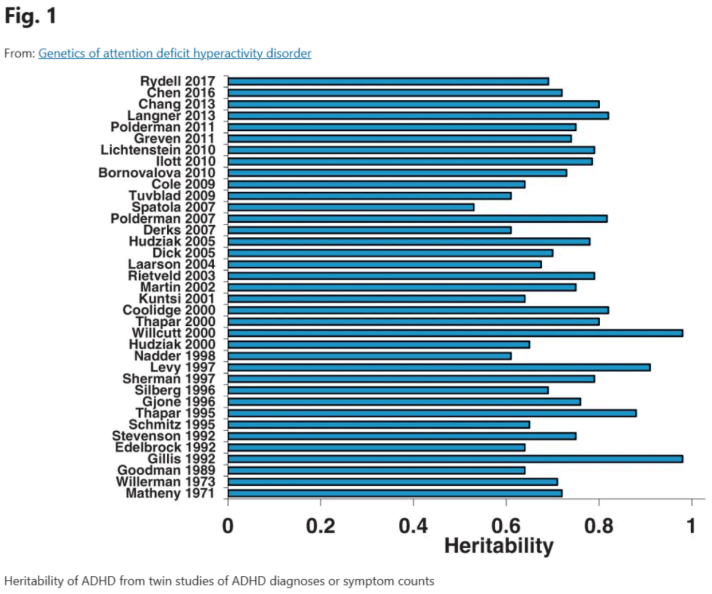

Figure 1. Bar chart showing the heritability of ADHD across multiple studies.

While the heritability of ADHD is well supported, it is also worth noting that a reporter effect has been seen in self-reporting. In this case, the incidence of self-rating of ADHD symptoms with different teachers of a twin pair showed lower heritability, around 30-40%, than with the same teachers of a twin pair showed a heritability around 70-80%. Of course, this difference could be because of different raters for each twin, which could have introduced effects where the rater experiences different ADHD symptoms (Faraone, 2019).

The Search for the ADHD Gene

After the positive results of the heritability of ADHD, the search for a gene began. This started with genetic linkage studies, which found linkage on chromosome 16. Then, using linkage across multigenerational populations, evidence was found indicating chromosomes 4, 5, 8, 11, and 17 (Faraone, 2019). Then, a candidate gene association study (CGAS) was done to try and find a specific gene. CGAS are studies that use knowledge about biology or biological function to target specific genes they hypothesize might be of interest. After doing a CGAS, there were 6 genes found: serotonin transporter 5HTT, dopamine transporter DAT1, dopamine receptor DRD4, dopamine receptor DRD5, serotonin 1B HTR1B, and a synaptic vesicle regulating protein SNAP25 (Faraone, 2019). What can be seen from these studies is that it is not known what exact gene causes ADHD, nor where this gene is located. However, the CGAS did give researchers some possible genes to start with for in their ADHD research.

Genome-wide association studies (GWAS) are similar to CGAS except that they look across the entire genome and see if there are genetic variations that are found in those with ADHD versus those without ADHD. A meta-analysis with 2455 controls, 896 people with ADHD, and 2064 trios of two parents and an ADHD child found no significant genes. Overall, GWAS shows that a significant portion of the heritability of ADHD was due to the influence of multiple genes that all have a small effect. A specific single-nucleotide polymorphism was found to have a heritability of 22%, making up a third of the heritability found in twin studies. This multi-gene theory was confirmed by using a polygenic risk score that predicted ADHD. In even more support for the multi-gene theory, it discusses how certain polymorphisms are located in places in the genome that are important for brain function (Faraone, 2019). The difficulty of a disorder like ADHD is that while multiple genes are likely to be involved, genetic studies are still unable to determine which genes are involved and to what extent.

Promising ADHD Genes

Despite the lack of specific data on the genetic cause of ADHD, there has been a lot of research investigating certain genes and pathways that could be involved. Bidwell et al. discuss three specific genes of interest: the dopamine receptor gene (DRD4), the dopamine transporter gene (DAT1), and the serotonin transporter (5HTT).

Bidwell et al. first start with the dopamine receptor gene, DRD4. The DRD4 gene is located on chromosome 11 and is interesting because DRD4 receptors are expressed in regions associated with attention and inhibition. Many studies have specifically looked into a 48-base-pair variable repeat polymorphism in a specific exon that codes for a loop around the receptor. Generally, the 4-repeat polymorphism is most common in the population, but the 7-repeat allele has been associated with ADHD. In response to this change, research has been focused on testing whether this difference in repeats has made a difference in the efficacy of drugs, but there have not been consistent

results in this kind of testing (Bidwell, 2011). Another reason that dopamine is of interest to those studying ADHD is because of how many brain functions dopamine signaling is involved in.

Another gene of interest is the dopamine transporter gene, which is located on chromosome 5. This gene is of specific interest because it is heavily expressed in the striatum, a region of the brain associated with attention, working memory, reward, and decision-making, where its main function is to reuptake dopamine. Additionally, this gene is interesting because dopamine transporters are the primary site that stimulants used to treat ADHD target. The most popular polymorphism is a variable repeat that is found in the untranslated region of the DAT1 gene. Untranslated regions are part of the genome that are not translated into protein, so these untranslated regions do not affect the protein of the dopamine transporter. However, the significance of this sequence is that it is believed to affect the expression of the dopamine transporter (Bidwell, 2011). Overall, this gene is significant because it can affect the dopamine levels in the brain regions associated with attention, memory, etc, which could cause some of the symptoms commonly seen in ADHD.

Another gene that Bidwell et al. focus on is the serotonin transporter gene (5HTT). Unlike the dopamine-associated genes, the role of serotonin has been less studied. Where this 5HTT has been promising is in animal studies that show serotonin having a key role in regulating things like attention. Additionally, when this transporter has been disrupted, there has been an increase in hyperactivity in mice. This is interesting, as one of the hallmarks of ADHD is hyperactivity. Similar to the DAT1 gene, the polymorphism of interest is associated with changes in transcription and activity of the transporter. Specifically, this polymorphism is a 44-base pair deletion in the promoter region of the gene. The function of promoter regions is to regulate the transcription of specific genes. With this specific change, researchers see less transcription and a reduced amount of the transporter itself (Bidwell, 2011).

Given the data on the three genes, Bidwell et al. performed a family-based association test (FBAT) on the polymorphism surrounding the DRD4, 5HTT, and dopamine transporter genes. They then performed testing to determine how often that variance was associated with either overall ADHD or a certain symptom, like inattention or hyperactivity/impulsivity. This data can be seen in Table 4 from their paper. What they found was that the DRD4 gene was statistically significant for all types of ADHD compared to. Additionally, they found statistically significant results with the dopamine transporter gene when comparing against total ADHD and the inattentive phenotype. However, this result was not seen in the hyperactive/inattentive phenotype (Bidwell, 2011). These results from Bidwell et al. are significant as they could give further insight into a specific polymorphism in a particular gene that is associated with ADHD. It also provides a guide for further studies to repeat this analysis and to compare with different polymorphisms.

Table 4 Results of FBAT statistics for each candidate polymorphism and the total ADHD and dimensional symptom phenotypes

From: A Family Based Association Study of DRD4, DAT1, and 5HTT and Continuous Traits of Attention-Deficit Hyperactivity Disorder

Polymorphism	Informative families	FBAT-GEE					
		Total ADHD		Inattentive		Hyperactive/impulsive	
		p-value	Variance explained	*p*-value	Variance explained	*p*-value	Variance explained
DRD4 exon III VNTR							
4-repeat	160	.007 +	.01	.007 +	.01	.003 +	.01
7-repeat	122	.05 -	.01	.21	.01	.08	.01
DAT1 3′ UTR VNTR							
9-repeat	139	.03 -	.00	.009 -	.01	.57	.00
10-repeat	141	.02 +	.01	.005 +	.02	.47	.00
5HTTLPR							
Short	110	.23	.00	–	–	–	–
Long	110	.23	.00	–	–	–	–

"+" Indicates allele is positively associated with phenotype, "-" Indicates allele is negatively associated with phenotype
Bold indicates statistical significance at a level of $p < .05$

Figure 2. Table with FBAT results for each polymorphism and related ADHD phenotype with significance value.

Despite any controversies surrounding ADHD, the research has shown that this is a multifaceted disorder. Unlike many other disorders or illnesses, no one gene can explain the cause of ADHD. However, whatever factors influence this disorder have a strong genetic component that can be observed in heritability studies. The many different hypotheses of the root cause of ADHD include problems with dopamine and serotonin. Further research could test combinations of genes and ADHD. These studies could investigate whether a change in activity in both the dopamine and serotonin genes is correlated with increased ADHD symptoms. This could help understand the likely polygenic aspect of ADHD.

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About the Author

Meredith Kremitzki is a junior at the University of Illinois, majoring in psychology with a concentration in cognitive neuroscience and a minor in integrative biology. She became involved with Brain Matters to learn more about the different topics in neuroscience. Along with writing for Brain Matters, Meredith is a laboratory teaching assistant for the chemistry department. She hopes to become a doctor and continue learning about the brain and body.