Analysis of the Evolution of Attention Deficit/Hyperactivity Disorder and Its Effect on University Students

Submitted by

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Abstract

Attention Deficit / Hyperactivity Disorder (ADHD) is defined by the CDC as a neurodevelopmental disorder which can cause inattentiveness, impulsivity, and hyperactivity (Centers for, 2021). While this disorder has been studied from many angles, including characterizing the symptoms through many age groups, its causes from a genetic and environmental perspective, and what treatments can be most effectively used to treat people with it, one perspective that goes commonly unused is to view the disorder from an evolutionary perspective. Using data from genome-wide association studies such as the IMAGE project, two candidate genes were identified for association with ADHD (DRD4 and DAT1) which served as the basis for the study of the evolution of ADHD (Brookes et al., 2006). With the data on these genes pulled from the NCBI, GenomAD, ClinVar, and OMIM databases, the Evolutionary history of the variants of these genes which have shown statistical significance in their association with ADHD were analyzed. With that information, multiple testable hypotheses as to which situations and problems people with ADHD may have evolved to be better equipped to handle in the modern day were generated for testing in Alexis Albright's section of this study.

Introduction

ADHD is a neurological disorder most commonly diagnosed in children and commonly lasts long into adulthood. Symptoms of this disorder can present themselves in a wide variety of ways but can be categorized into one of three categories, inattentive, hyperactive, or a combination of both. According to the CDC, the inattentive type presents itself in an individual who finds it difficult to "organize or finish a task, pay attention to details, or to follow instructions and conversations. The person may also be easily distracted or forgets details of daily routines" (Centers for, 2021). The second way that ADHD presents itself is the

Hyperactive-Impulsive type, which according to the CDC is observed as a person who finds it hard to sit still for long periods of time, perhaps by fidgeting or moving around. This may present itself in small children as constant running, jumping, climbing, or moving around when they are attempting to do a task. The individual may also feel restless and have problems with being impulsive which is the other category of symptoms presented in this ADHD variant. A person who is impulsive may interrupt others during conversations, grab things from people, or speak at inappropriate times. They may also find it difficult to wait their turn or listen to directions being given to them, or also find that they have more accidents or injuries than their peers (Centers for, 2021). The third and final category is where a person shows a combination of symptoms from both the inattentive and hyperactive/impulsive categories. The causes for ADHD are also currently being studied but it is widely accepted that ADHD has both genetic and environmental causes. The exact proportion of cases that are caused by genetics or environmental causes is difficult to determine, however, there have been studies which suggest that the heritability of ADHD has a heritability of 74%, showing that genetics does have a significant role in the etiology of the disorder in addition to environmental factors (Faraone & Larsson, 2018). Due to this complexity in accurately understanding the causes and the wide variety of ways that ADHD can present itself in a patient, it is a complex process to diagnose a patient with ADHD. This process has historically included a checklist for rating the different types of symptoms and taking histories from the child, the child's parents, or the child's teachers. According to recent studies, ADHD affects 2.2% to 17.8% of all school-aged children and adolescents, having a disproportionately higher effect on boys (10.60%) than girls (5.28%) (Ayano et al., 2020). The most common form of ADHD has also been observed to be the inattentive form, followed by the hyperactive-impulsive type, and lastly by the combined type

with 2.95%, 2.77%, and 2.44% prevalence respectively (Ayano et al., 2020). As a result of the symptoms experienced by these patients and the potential different means of coping with the symptoms, ADHD can often lead to secondary symptoms like anxiety, depression, sleep problems, or may even be viewed as a learning disability, which leads to the hypothesis behind this study (Centers for, 2021). While this disorder has been studied from many angles, including characterizing the symptoms through many age groups, its causes from a genetic and environmental perspective, and what treatments can be most effectively used to treat people with it, one perspective that goes commonly unused is to view the disorder from an evolutionary perspective. ADHD is a trait that has changed its frequency in different populations throughout human history. By analyzing the populations who have shown a marked increase in ADHD, analyzing the frequency of the genes and variants of those genes which are known to cause ADHD, and the different situations that those populations found themselves in, we may be able to glean from that information possible circumstances in which humans were under evolutionary pressure for ADHD to increase in frequency, and as such the types of circumstances and problems which ADHD is advantageous, or at least not detrimental to the individual or community. Armed with that information, we can then find situations or problems which are similar in nature and (in another survey undertaken by Alexis Albright) find out if those with ADHD still are better equipped to handle those types of problems and circumstances compared to their peers in modern schools and universities found in western countries.

Genome-Wide Association Studies

The first step in being able to view ADHD from an evolutionary perspective is to find which genes are associated with or cause the disorder. The reason for this is twofold, any trait cannot be acted upon by evolutionary forces if it is not caused by or affected by genetic factors.

Secondly, if it is caused or affected by genetic factors, then we need to identify the genes or mutations which cause or are risk factors for ADHD because it is those variants themselves that we will then analyze to formulate any conclusions. One way which has become feasible in the past couple of decades due to new advances in DNA sequencing technologies is to identify genes or mutations which are associated with a given trait by using what is known as a genome-wide association study (GWAS). What this type of study entails is to take a large group of individuals, group them into two test groups, one consisting of people who have your trait of interest, in our case, it is people who have been diagnosed with ADHD, and another group which will serve as the control, which in our case is people who don't have ADHD but are close relatives to those in the experimental group to minimize genetic differences. Then once these groups have been established, their entire genomes will be sequenced using next-generation DNA sequencing. That data will then be processed by computers to find if any specific mutations or variants of certain genes were found to be statistically correlated to those who had ADHD compared to those who didn't (Brookes et al., 2006). If variants are found to be statistically significant in their correlation to ADHD, then those variants are known to at least be associated with the disorder and then become candidates for further study to understand that correlation. However, if the trait being studied is more complex and has a lot of factors that go into the causes such as outside environmental factors, then there may not be any variants that come up as statistically significant. The largest study to date using this procedure to study ADHD was known as the International Multicentre ADHD Genetics (IMAGE) study which was looking at 51 possible candidate genes that may be associated with ADHD. The study used 674 children who were diagnosed with DSM-IV ADHD who had at least one full sibling (N=808) and both biological parents (N=1228) available to conduct a GWAS study and found that 18 of the genes, as shown

in Figure 1, showed evidence of variants that were statistically significant in their association with ADHD, which included two of the most replicated findings in the literature: the dopamine D4 receptor gene (DRD4) and the dopamine transporter gene (DAT1, DAT, SLC6A3) (Brookes et al., 2006). These two genes being the most well-studied and researched in the field for association with ADHD will serve as the basis for understanding possible situations in which ADHD might have evolved.

The Dopamine D4 Receptor Gene (DRD4)

The first gene of interest which was analyzed was DRD4. DRD4 is a gene found on the 15th band of the p arm of chromosome 11 (11p15) which is 8.4kb in length, and codes for a transmembrane protein known as dopamine D4 receptor, which according to the National Center for Biotechnology Information, is a G-Protein coupled receptor which inhibits the action of adenylyl cyclase (U.S. National Library of Medicine, 2023). What this means is that this receptor will sit in the plasma membrane of the cell within which it was produced waiting for dopamine or dopamine agonists to bind to its active site. Once this happens, as can be seen in Figure 2, the receptor will undergo a conformal change in its structure which will activate a coupled G-protein as the name implies. G-proteins are proteins which bind the nucleotides guanosine triphosphate (GTP) and guanosine diphosphate (GDP) which when the protein is activated will release a phosphate group. This conformal change will go down a biochemical pathway which, depending on many different factors such as the cell it was on, which pathway that specific receptor is a part of, and other such factors will go on to affect other changes inside the cell (Nature Publishing Group, 2014).

The exact Biochemical pathway through which variations or mutations in the DRD4 gene may cause ADHD is still not fully understood, however, researchers theorized based on the

known functions of DRD4 a few possible pathways through which variants of DRD4 could lead to the symptoms observed in all versions of ADHD. To understand these theories, firstly we must understand the specific variants of the DRD4 gene which have been associated with ADHD. The most studied of these variants is referred to by researchers as the 7-repeat allele (7R). This variant is a variable number tandem repeat mutation (VNTR) consisting of a 48-bp repeating unit in Exon III of the DRD4 gene as can be seen in Figure 3. These 48bp have been observed to repeat anywhere between 2-11 times in varying degrees of accuracy, meaning perfect repetition may not be observed and there may be a few differences between repeat to repeat, with the most common forms being the 4, 7, and 2 repeat alleles with global mean allele frequencies of 64.3%, 20.6%, and 8.2% respectively, with the 7R allele showing the highest level of association with ADHD and as such has been the most studied amongst researchers (DiMaio et al., 2003). The theory behind the etiology of ADHD through the DRD4 7R allele is that it has been shown in mice that these variants have been reported to produce a protein product of DRD4 which shows a lower affinity to dopamine than the non-mutated version (Ptácek et al., 2011). This lowered affinity to dopamine and dopamine agonists has been studied as a contributing factor to ADHD and results suggest that the long allele of DRD4 (7 repeats or more) is associated with high novelty seeking, risk-taking, constricted emotional responses, but is also associated with preserved attention processing of emotional stimuli and efficient problem solving (Ptácek et al., 2011). Other studies showed that when the mice were treated with an injection of Dopamine agonists, the mice displayed an increase in frequency and duration of ‘spontaneous exploratory activity and also facilitates the initiation, speed, and vigor or locomotion’ (Chen et al., 1999; Fink & Smith, 1980). Due to the large amount of research that has been conducted on the association between DRD4 and ADHD, it has been found throughout many different GWAS,

meta-analyses, linkage, and twin studies that while there is a definite association between DRD4 and ADHD, there is some debate as to how strong that association is. While projects such as the IMAGE project found a significant association between the gene and the disorder, some studies like the one conducted by Faraone et al. had results from a twin/family study that suggested that while there was an association between DRD4 and ADHD, that it was a small association, and they called for more future studies to be able to more intricately study of the link between the two (Faraone et al., 2001). Despite the debate as to how closely associated DRD4 and ADHD are, there was a gap in the research as to which populations across the globe most displayed this VNTR polymorphism, and more importantly, if humans also showed an increased amount of novelty-seeking and exploratory behavior in association to the mutation, specifically the 7R allele. One meta-analysis of all of these studies was compiled by studying the data from 12 separate studies which examined a total of 4,640 alleles of 2,320 individuals from 39 different populations and used the data to analyze the correlation between these behaviors and the distribution of the allele frequencies for DRD4, and specifically the 7R Allele (Chen et al., 1999). The results from that study can be seen in Figure 4, which as the researchers went on to show in their meta-analysis, show that there was a very strong association between the proportion of long alleles of DRD4 and its prehistoric macro-migration histories. According to the researchers, “the populations that remained near their origins showed a lower proportion of long alleles of DRD4 than those that migrated farther away” and that finding was consistent across all six migratory routes which they analyzed (Chen et al., 1999). This led the researchers to conclude that since they could rule out spontaneous mutation and genetic drift due to the strong association between migration and allele frequencies of the DRD4 gene, and the fact that they showed that founders’ effect cannot adequately explain the global distribution of the long

alleles of DRD4, that the data from their own study and the 12 studies which they pulled their data from, seemed to favor the natural selection/deselection hypothesis. This hypothesis was that the long alleles of DRD4 were selected for in migratory societies because of the increased novelty-seeking personalities, hyperactivity, and risk-taking behaviors observed in individuals with the mutation (Chen et al., 1999). They suggest that in light of this data, "it can be reasonably argued that exploratory behaviors are adaptive in migratory societies because they allowed for more successful exploitation of resources in the particular environment migration entails - usually harsh, frequently changing, and always providing a multitude of novel stimuli and ongoing challenges to survival" (Chen et al., 1999).

The dopamine transporter gene (DAT1)

The second gene of interest which was identified to be associated with ADHD and has been widely studied is the DAT1 gene, which has also been referred to as DAT, or SLC6A3. The gene for DAT1 is 64kb long, contains 15 exons, is located on chromosome 5p15.3, and is widely found in regions of the brain containing lots of dopamine signaling such as the striatum, nucleus accumbens, anterior cingulate, posterior parietal cortex, and hippocampus (Bédard et al., 2010; Ciliax et al., 1999). DAT1 codes for a transmembrane protein which is expressed in the synaptic ends of a neuron, much like DRD4. However, where DRD4 coded for a protein on the post-synaptic neuron that acts as a receptor for dopamine, DAT1 codes for a pre-synaptic co-transport transmembrane protein which serves as the primary means of reabsorbing dopamine back into the cytosol of the pre-synaptic neuron as can be seen in Figure 5, and acts as the main way for dopamine being cleared out of the extracellular matrix in the synaptic cleft. The secondary means of doing so is the simple diffusion of dopamine away from the synapse

through the extracellular matrix (Bédard et al., 2010). DAT1 can also be phosphorylated and act as a means of releasing dopamine into the synaptic cleft as a result of electrical activity and L-type Ca^{2+} channels (Cameron et al., 2015). The main variant of DAT1 that researchers have focused on is a VNTR in the 3' untranslated region (UTR) of exon 15. This VNTR polymorphism consists of a 40-bp unit repeat which has been observed to repeat anywhere between 3-11 times, the most common of which are the 9 repeat (9R) and 10 repeat (10R) alleles. There have been many association and linkage studies of these variants of the DAT1 gene as can be seen in Table 1, which were investigating the association between DAT1 and ADHD. Due to ADHD's polygenic nature and the effect of environmental factors, much like DRD4, there are mixed results as to whether or not DAT1 can be implicated in the etiology of ADHD, however, due to some physical experiments with DAT1 knock-out mice and the efficacy of a drug called methylphenidate in treating ADHD-like symptoms, DAT1 is considered to be amongst the most likely genes to be considered as genetic factors of ADHD (Giros et al., 1996; Storebø et al., 2018). Firstly, looking at the study conducted by Giros et al., they produced mice which had both copies of their DAT1 gene knocked out of their genomes by means of homologous recombination. These homozygous mice were then compared to mice which had both copies of their DAT1 genes, and also mice which were heterozygous for the mutation and noted the effects of psychostimulants such as cocaine and amphetamine on the behavior of the mice. These substances act by competitive antagonism to inhibit the function of DAT1 as the primary means of clearing dopamine out of the synaptic cleft, and as a result, mice which had both copies of DAT1 removed showed little to no effects on their behavior prior to administration, which were characterized as heightened spontaneous locomotion and other symptoms reminiscent of the traits observed in those with ADHD, compared to the mice which had both copies of the DAT1

gene which demonstrated a significant change in behavior upon administration of the drug. In Addition, the homozygous mice were found to have dopamine remaining in the synaptic cleft 100 times longer than either the heterozygous or the wild-type mice (Giros et al., 1996). These results, they explain, demonstrate that DAT1 is the most critical component in terminating dopamine neurotransmission. The reason this is important is that it has been demonstrated that decreased levels of synaptic dopamine have been linked to ADHD (Volkow et al., 2007). Therefore, the theory behind the etiological mechanism behind the 9R and 10R alleles is that since these variants have been associated with greater levels of dopamine transporter (Brookes et al., 2007; VanNess et al., 2005), and because the VNTR is found in the 3' UTR region of the gene, there is likely a change in the mRNA stability or protein translation leading to an increased level of DAT1 proteins being created and present in the membranes of pre-synaptic neurons, leading to the heightened levels of dopamine uptake back into the cytosol, and the decreased levels of synaptic dopamine which are linked to ADHD and it's related observed behaviors such as hyperactivity, novelty seeking, and risk-taking. (Bédard et al., 2010; Volkow et al., 2007).

In order to investigate the evolutionary history of the 3' VNTRs of DAT1, Two separate studies of the behavioral effects of individuals with the variant will be analyzed. The first of the two is a study conducted on a sample of more than 2500 individuals which found an association between the 9R and 10R alleles and self-reported number of sexual partners among young adults in the United States from the National Longitudinal Study of Adolescent Health. They note that there was a significant difference in frequencies of the 9R and 10R alleles between females and males which lines up with the evolutionary theory that for females, "every copulation might have led to conception, followed by lengthy periods of child-bearing and child-rearing; having more sexual partners would not increase female fitness" whereas in males, individuals would only

increase their fitness by increasing the number of sexual partners because they would not be contributing similar resources and time (Guo et al., 2007). This suggests that DAT1 serves a role as part of the dopaminergic pathway involved in promiscuity and that early on in human evolution, perhaps even as primates, being a male and possessing either the 9R or 10R alleles would confer an advantage to individual fitness amongst a population. The other study which will aid in analyzing the evolutionary effects of these variants of DAT1 is a study conducted on three different species of primates, including humans, cynomolgus macaques, and rhesus macaques which sought to analyze the sequence variation and extent of linkage disequilibrium (LD) across the DAT1 gene between the three species in an attempt to better understand the evolutionary history of the 9R and 10R alleles. They found that there was a significant association between both alleles, social rank in cynomolgus monkeys, extraversion in humans, and the analogous trait in monkeys which is social dominance. This suggests that the DAT1 gene conferred an advantage to individuals in highly social communities among humans and their primate ancestors (Miller-Butterworth et al., 2008).

Hypotheses for Testing in Alexis Albright's Survey

Having now identified the environments, situations, and problems which individuals with the variants of DRD4 and DAT1 associated with ADHD may have been better suited to deal with throughout human history, we can now begin creating hypotheses for the possible situations which those may compare to in modern day so that they may or may not be corroborated by survey data in Alexis Albright's section of this research. Starting with DRD4, we can hypothesize that people with ADHD may be better suited to dealing with problems that consist of an exploratory aspect of some kind, situations that may benefit from quick decision-making, impulsivity, and looking for new ways to solve problems or new perspectives due to their high

novelty-seeking behaviors, perhaps positions of leadership or positions where they can express their creativity in problem-solving. Looking at the traits observed in those who have the 9R and 10R alleles of DAT1, we can hypothesize that people with ADHD may be better suited to dealing with highly social situations, be more extroverted, or perhaps thrive dealing with problems which include the management or collaboration of multiple other individuals. People with ADHD may also suffer more from unplanned pregnancies, or have higher numbers of sexual partners than individuals without ADHD.

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Table 2 Table of results for the 18 genes found to be suggestive of association in the SNP screen

Gene	*Nominal* P-*value*	*T*	*NT*	*OR*	*Global* P-*value*	*P_SUM Statistic*
TPH2	0.003	207	151	1.37	0.036	0.106
ARRB2	0.004	103	66	1.56	0.022	0.209
DAT1	0.005	349	278	1.26	0.119	0.014
PNMT	0.008	70	42	1.67	0.012	0.024
SLC9A9	0.01	74	46	1.61	0.485	0.114
NET	0.012	133	95	1.4	0.349	0.786
ADRB2	0.013	210	162	1.3	0.088	0.485
HES1	0.016	300	244	1.23	0.076	0.096
ADRA1A	0.017	283	229	1.24	0.443	0.387
PER2	0.017	31	15	2.07	0.124	0.419
MAOA	0.02	175	134	1.31	0.082	—
SNAP25	0.035	155	120	1.29	0.529	0.198
DDC	0.039	161	126	1.28	0.537	0.597
FADS2	0.039	284	237	1.2	0.389	0.727
SYP	0.045	180	114	1.25	0.034	—
CHRNA4	0.05	116	88	1.32	0.503	0.663
HTR1E	0.051	75	53	1.42	0.509	0.214
DRD4	0.055	34	20	1.7	0.199	0.321

Nominal *P*-value is the most significant SNP from UNPHASED analysis with the relevant number of transmitted (T) and nontransmitted (NT) alleles from heterozygote parents. Odds ratios (OR) and the significance values for the two gene-wide association tests are listed (Global-*P* and *P*-SUM). *P*-SUM could not be calculate for X-chromosome markers

Figure 1. Table 2 from the Brookes et al. paper on data from the IMAGE study listing all the genes that were found to have variants that were shown to have statistical significance in their association with ADHD including DRD4 and DAT1 (Brookes et al., 2006).

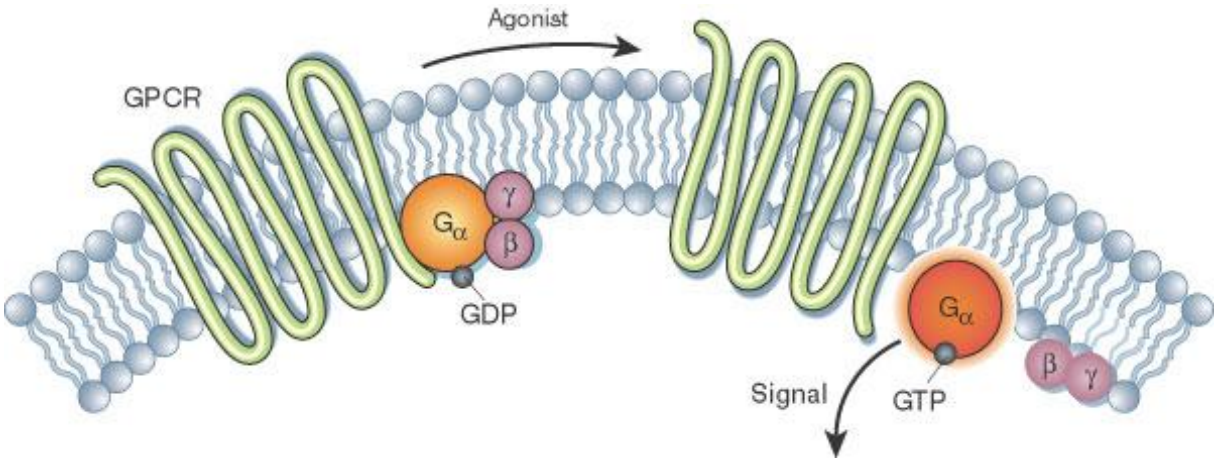

Figure 2. The activation of an αG-protein coupled receptor and the conformal changes that take place thereafter leading to a biochemical cascade further down in whichever cellular process this receptor is linked to, in this case, it's a Dopamine receptor in neurons found in the brain (Nature Publishing Group, 2014).

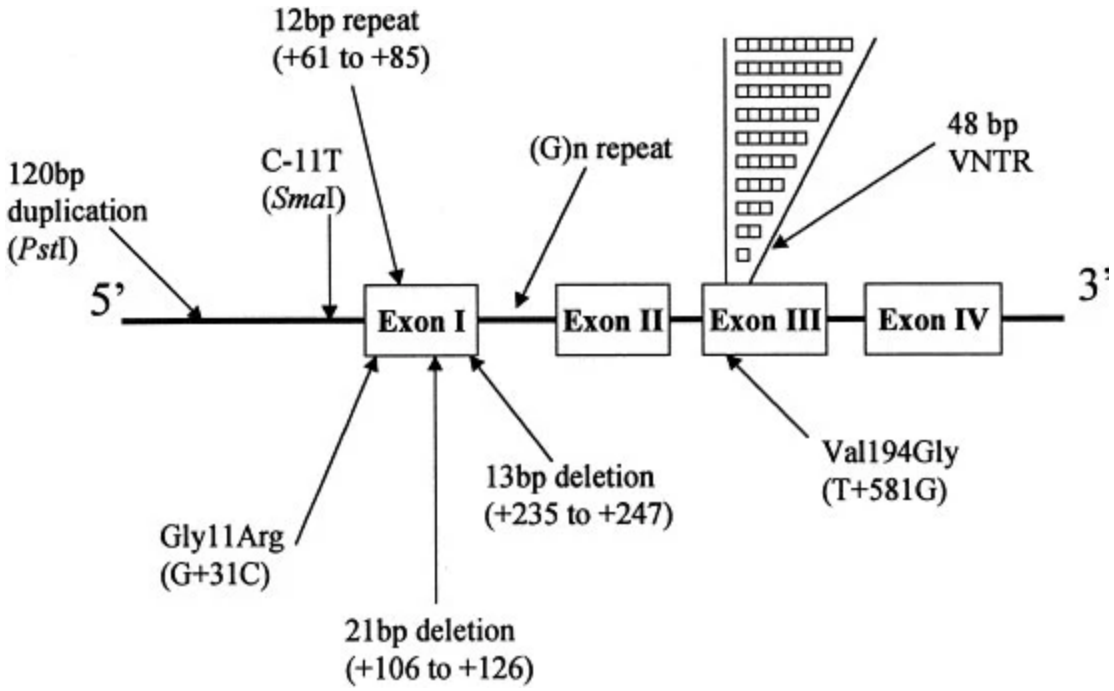

Figure 3. Diagram of the section of DNA coding for the DRD4 gene with the polymorphic sites which have been identified. The one we are interested in is the 48bp VNTR polymorphism site in exon III of DRD4 which has been associated with ADHD (Paterson et al., 1999).

Population	Locations[a] (long.; lat.)	Macro-migration (in k miles)	7-repeat (%)	long alleles (%)	Sample size (2n)[b]
(a) Migration from Northern Asia to Americas					
Jemez Pueblo (U.S.)	36N; 107W	6.5	19	25	86
Cheyenne (U.S)	35N; 99W	6.6	34	47	96
Pima (U.S.)	33N; 112W	6.7	22	25	70
Muskoke (U.S.)	33N; 84W	7.1	29	33	24
(North Americans averaged)		(6.7)	(26)	(32)	
Mayan (Yucatan)	19N; 91W	8.6	39	42	100
Guahibo (Colombia)	8N; 73W	9.9	62	77	26
R. Surui (Brazil)	11S; 62W	10.6	69	70	90
Quechuan (Peru)	12S; 77W	11.1	45	59	44
Karitiana (Brazil)	10S; 63W	11.2	60	61	108
Ticuna (Colombia)	3S; 70W	11.3	78	78	128
(South Americans averaged)		(10.8)	(63)	(69)	
(b) Migration from China					
Han (China)	—[c]	0.0	0	5	576
Atayal (Taiwan)	23N; 122E	0.8	0	4	56
Ami (Taiwan)	23N; 122E	0.8	0	6	76
Japanese	30–40N; 103–145E[d]	1.4	1	6	814
Malay	3N; 100E	4.3	17	25	24
Samoans	14S; 172W	6.6	5	5	22
Micronesians	8N; 150E	6.7[e]	3	11	52
(c) Migration from Southeast Asia					
Papua New Guineans	5S; 145E	3.0	25	25	40
Nasioi Melanesians	4S; 154E	3.6	30	34	46
(e) Migration of Jews from Israel					
Yemen Jews	16N; 44E	1.2	0	0	74
Falasha (Ethiopia)	10N; 40E	1.8	11	14	124
Roman Jews	42N; 13E	2.3	19	23	44
Ashkenazi Jews (Israel)[f]	—	2.4	17	19	248
(f) Migration of African groups					
Biaka (CAR[g])	3N; 18E	0	14	24	50
Mbuti (Zaire)	1N; 29E	0	16	17	36
San (South Africa)	30S; 20E	0.5	0	9	80
Bantu (South Africa)	30S; 20E	4.2	19	34	28
(g) Indo-European groups with migration distance estimated from probable origin of language family					
Sardinians	40N; 9E	0.5	0	0	26
Danes	55N; 9E	1.0	14	16	64
Swedes	58N; 18E	1.0	16	19	130
Spanish	40N; 3W	1.0	18	18	136
Mixed Europeans (U.S.)	—[h]	1.0	16	22	542

Figure 4. Frequencies of the VNTR DRD4 polymorphism alleles and the macro-migration of a variety of different populations of early humans, including data on the 7R and other long alleles (Chen et al., 1999).

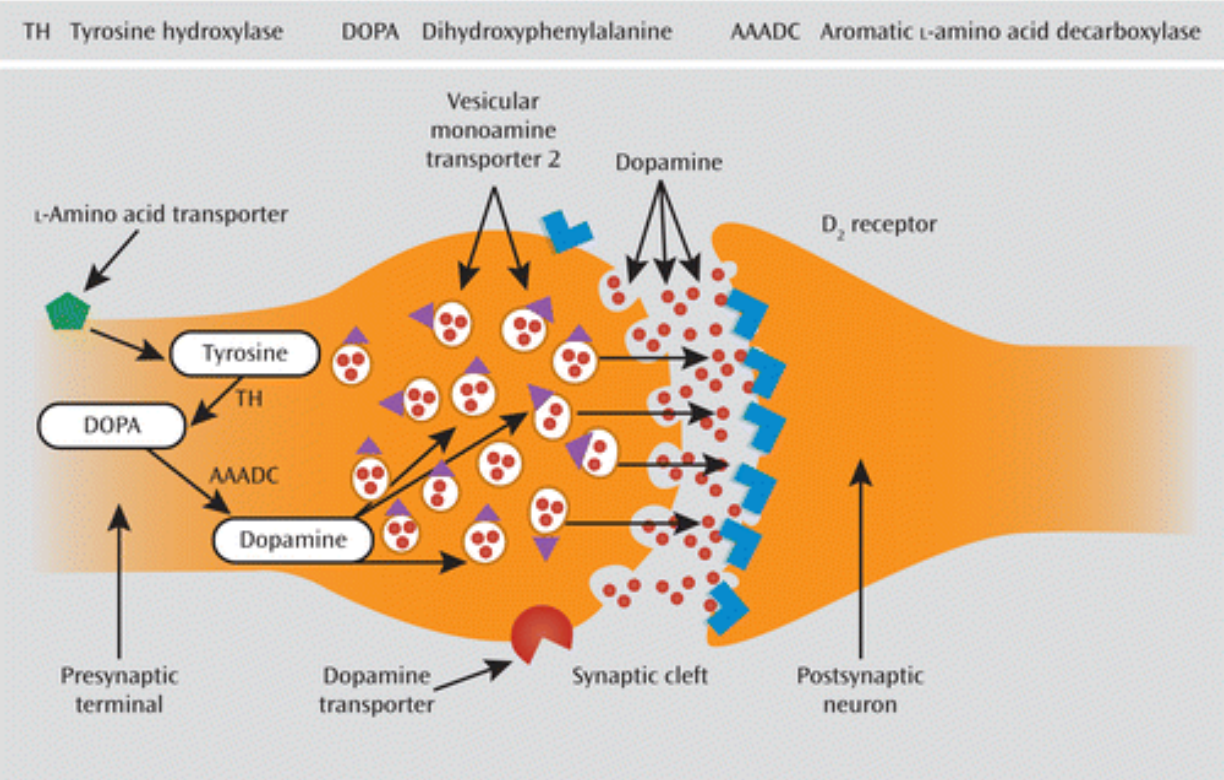

Figure 5. Simplified image of a dopaminergic synapse including the precursors to dopamine, dopamine transporter (DAT1), and Dopamine D2 receptors in the post-synaptic neuron (Fusar-Poli et al., 2012).

Table 1: Studies of the association between attention-deficit hyperactivity disorder (ADHD) and the *SLC6A3* 480-bp VNTR allele

Study	Location	No. of probands	Diagnostic system	Test of association	Linkage	Statistic	*p* value
Barr et al[27]	Canada	102	DSM-IV	TDT	–	$\chi^2 = 2.6$	0.06
Roman et al[28]	Brazil	81	DSM-IV	HHRR	–	$\chi^2 = 0.02$	0.88
Curran et al[29]	Turkey	111	DSM-IV	TDT	–	$\chi^2 = 0.93$	0.34
Curran et al[29]	United Kingdom	66	DSM-IV	TDT	+	$\chi^2 = 8.97$	0.001
Holmes et al[30]	United Kingdom	137	ICD-10, DSM-IV and DSM-III-R	TDT	–	OR = 0.89	0.59
Palmer et al[31]	United States	209	DSM-IV and DSM-III-R	TDT	–	OR = 0.88	0.40
Daly et al[32]	Ireland	118	DSM-IV	HHRR	+	RR = 1.2	0.006
Waldman et al[33]	United States	122	DSM-IV	TDT	+*	OR = 1.63	0.06
Cook et al[34]	United States	49	DSM-III-R	HHRR	+	OR = 3.17	0.01

Note: DSM = *Diagnostic and Statistical Manual of Mental Disorders*; TDT = transmission disequilibrium test; HHRR = haplotype-based haplotype relative risk; OR = odds ratio; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, Tenth revision*; RR = relative risk.
*For combined type only.

Table 1. This table from the DiMaio et al. paper lists multiple studies which sought to analyze the possible association between ADHD and the 9R and 10R alleles of DAT1.