u n d e r s t a n d i n g

ADHD GENETICS

WHAT IS **ADHD**?

ADHD is a complex condition with numerous associated genetic factors. However, the science around ADHD has significantly matured and evolved since its first conception. Today it is widely accepted by the scientific community as a serious medical condition, however it is still poorly understood by the general public.

MENTAL DISORDER[1]

NEURODEVELOPMENTAL

A mental health disorder defined in psychiatry as impairing levels of inattention and/or hyperactivity/impulsivity that are pervasive and frequent.

Diagnosis

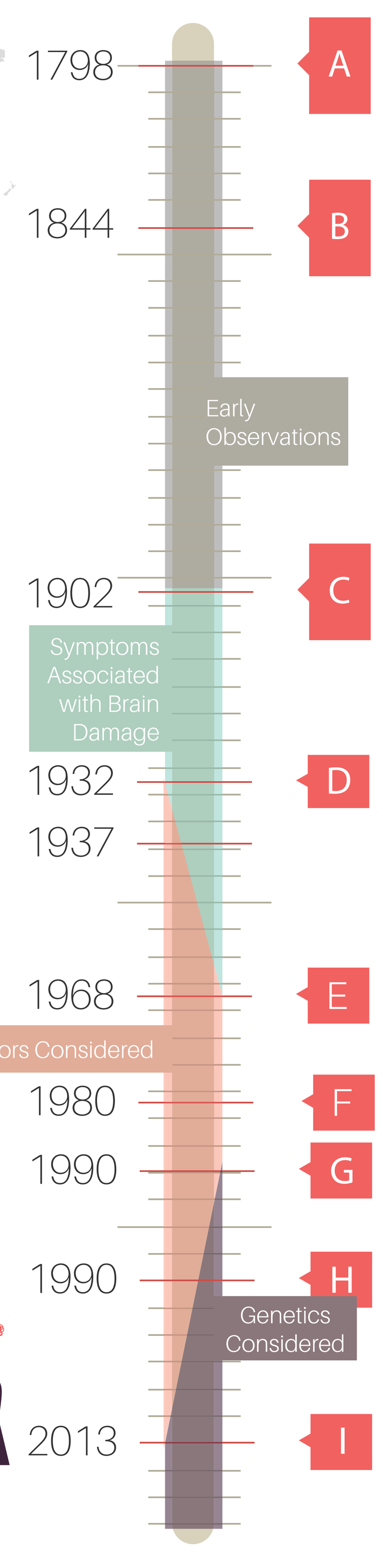
The criteria for diagnosis are based on the observation of persistent neurodevelopmental deficits that are having an observably negative impact in at least two-thirds of life circumstances (such as education, social integration, personal development, work, etc.) for longer than six-months[1].

AFFECTS ~5% OF PEOPLE WORLDWIDE[2]

Genetic inheritence a major contributor[1].

There is significant public concern about the over medication of children with ADHD.

Cognitive Therapy a promising alternative to psychostimulants[25]



Innattentive | Combined | Hyperactive/Impulsive

3 Sub Types[1]

PSYCHOSTIMULANTS THE #1 TREATMENT[8]

WORTH $7-9 BILLION by 2018[7]

Prenatal smoking exposure is a significant contributing factor[23]

ADHD can be described as a hypersensitivity that can lead to mental overload[14].

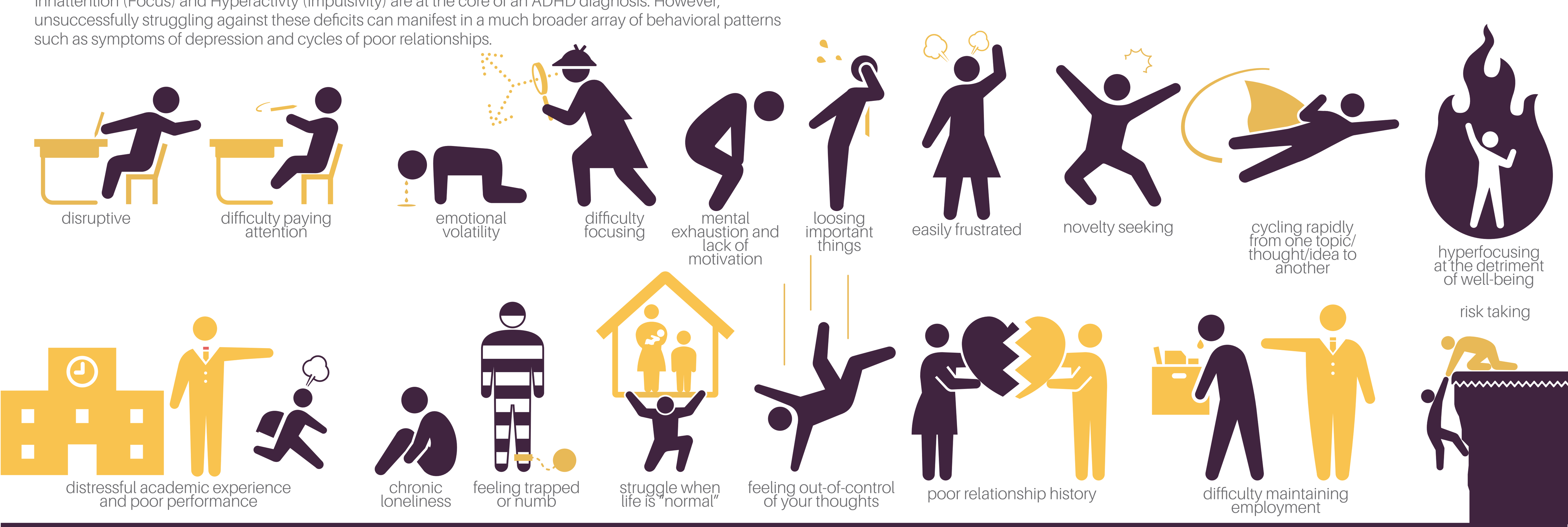
Boys are 8x more likely to be diagnosed than girls.

8 : 1

But it may have more to do with boys presenting as more hyperactive[22]

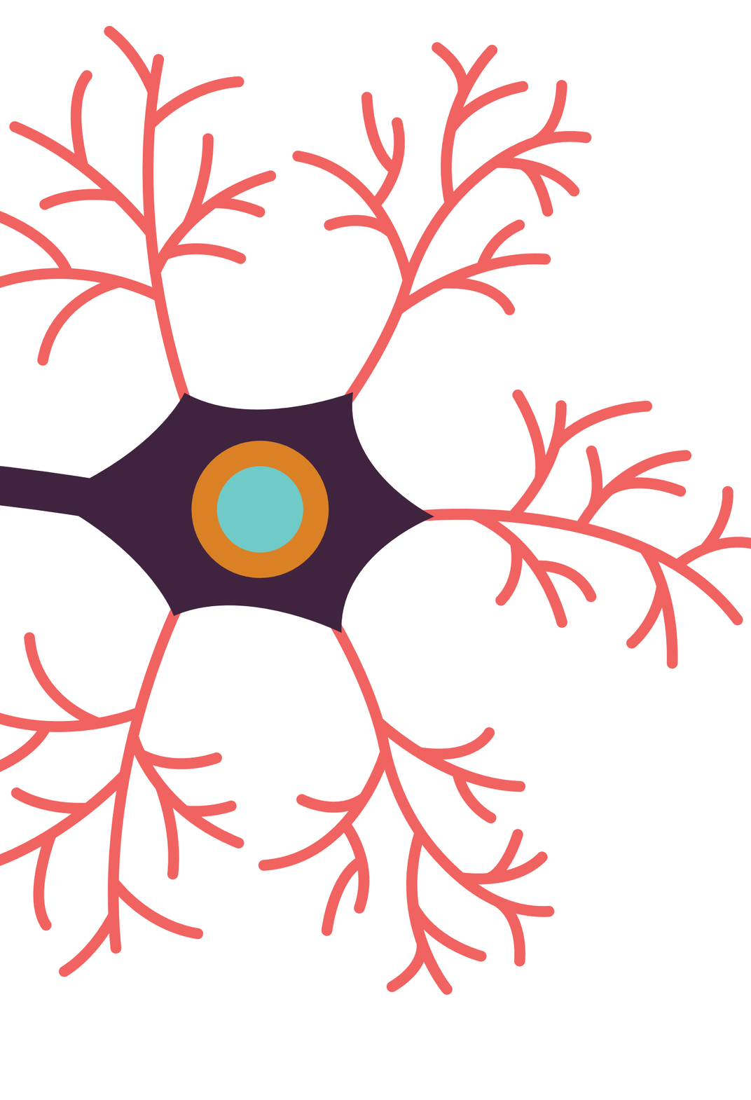
BEHAVIORAL **PATTERNS**

Innattention (Focus) and Hyperactivty (Impulsivity) are at the core of an ADHD diagnosis. However, unsuccessfully struggling against these deficits can manifest in a much broader array of behavioral patterns such as symptoms of depression and cycles of poor relationships.



BIOLOGICAL **INDICATORS**

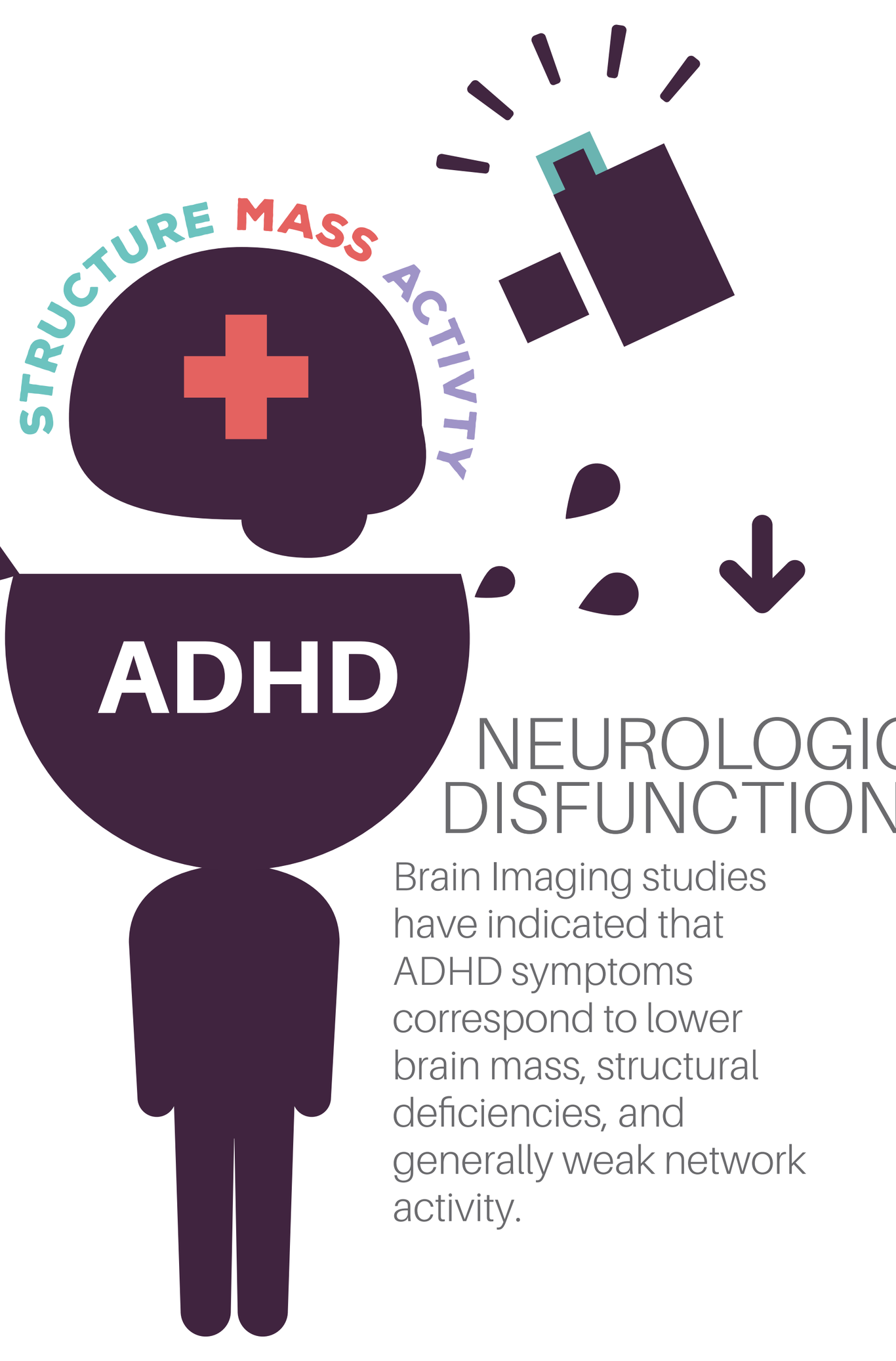
DOPAMINE DEFICIT[6]



Dopamine is powerful neurotransmitter that regulates the **sense of well-being** in response to appropriate stimulus. Studies suggest that ADHD patients lack sufficient dopamine receptors, and therefore are continually seeking to compensate.

Dopamine Deficiency is associated with novelty and "thrill" seeking as those suffering with the condition attempt to stabilise.

The effectiveness of psychostimulants, in low medicinal doses also suggests a strong link of DD to ADHD as these stimulants interact directly with dopamine by preventing its reuptake.



NEUROLOGICAL DISFUNCTION[14,20]

Brain Imaging studies have indicated that ADHD symptoms correspond to lower brain mass, structural deficiencies, and generally weak network activity.

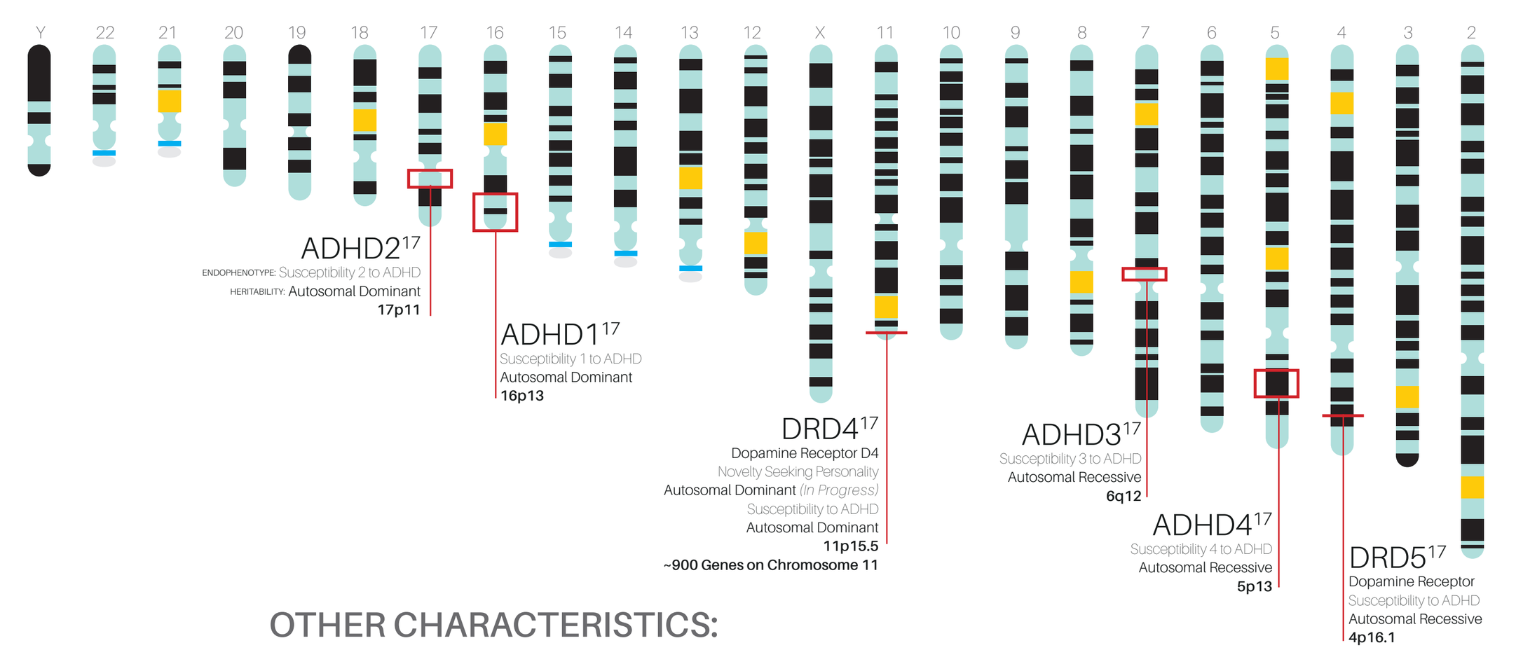
THE **GENETICS** OF ADHD

A Genetic Web

Studies have shown a wealth of positive genetic evidence in the ADHD population, which significantly supports the theory of biological inheritance; however this is combined with a great deal of variability and a lack of evidence for one unrefuttable candidate gene.

Numerous genes gave been implicated as possible "risk" candidates. Considering the association of ADHD with dopamine deficiency, it isn't surprising that a great deal of research has gone into finding links surrounding the production and absorption of this neurotransmitter. Nearly all candidate genes are largely contested, and therefore only the associated genes listed on the OMIM® databse as accepted gene relationships to ADHD have been included on the map at right.

This combination of a large body of genetic evidence and variable results suggest a number of advanced genetic concepts that go beyond the original Mendelian Laws. More research is required to establish the significance of these concepts in ADHD inheritance.



A Quantitative Trait[18]

The ADHD phenotype does not follow a threshold type expression, where the trait is either "on" or "off." It is expressed in a wide spectrum of severity and variability, and therefore genetic variability and complexity is expected.

Polygeneity[18]

When a disorder is caused by two or more genetic mutations. ADHD demonstrates links with multiple genes that contribute to susceptibility. Seven different genes have demonstrated the strongest correlation with the disorder, however there are numerous other that have also been implicated.

OTHER CHARACTERISTICS:

Influence Expression Variability

Incomplete Penetrance[18]

The effective quality of a mutation to exhibit a phenotype. If a mutation in a monogenic, autosomal dominant trait has a penetrance of 70%, than 70% of the carriers would be expected to express the phenotype.

Influence Gene Candidacy

G x E[18] (Gene - Environment Interactions)

How a phenotype can be expressed by different genotypes depending on environmental factors. "Growing Tall" is a phenotype that can be expressed by several different genotypes of one plant when grown at different elevations. Environmental factors such as prenatal smoking, psychological adversity, and even season of birth have been associated with increased expression of ADHD behavior. Therefore the numerous genotypes associated with ADHD may vary in their prominence depending on numerous environmental factors.

Epistasis[18]

When the expression and variability of a gene depends on the presence of another gene. ADHD has expressed some characteristics of epistasis, where the combination and co-presence of different ADHD related genes could create different levels of susceptibility or severity.

Pleiotropy[18]

When one gene can influence two or more unrelated phenotypes. This concept supports the interplay of multiple ADHD genes.

A Muddy Pool

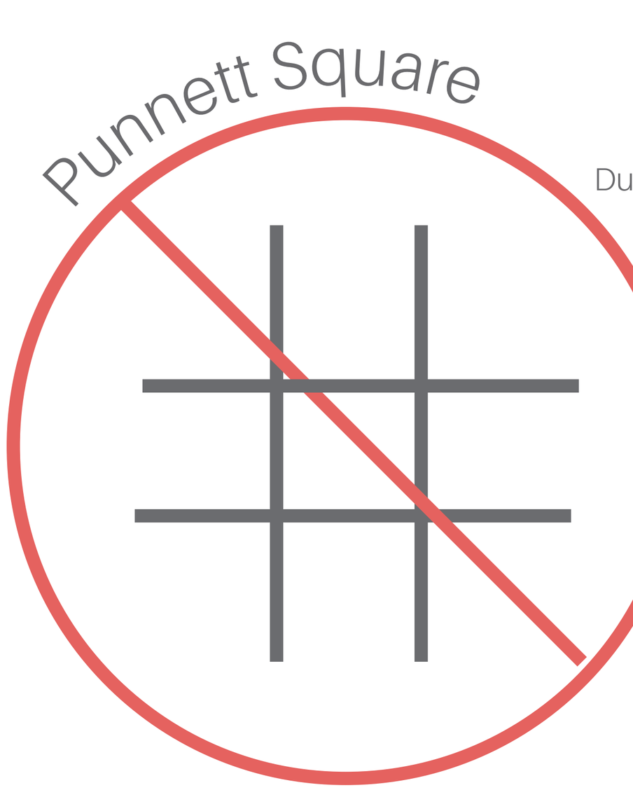
Meanwhile other factors related to the composition of studied populations of ADHD patients further complicates matters:

Evolution of Diagnostic Criteria[18]

The criteria used for ADHD diagnosis has been revised numerous times over the years and grown to include large parts of the population were not considered before. This makes gathering consistent long-term data inherently difficult.

Variation in Diagnostic Methods[18]

The methods used to diagnosis ADHD individuals vary from a single formal interview to a thorough and multi-dimensional analysis including third-party consultation, self-rating reports, educational assessment, neuroimaging scans, and psychological testing over an extended time-frame. Therefore it is hard to determine how accurately each individual in a study population can be compared to one another.



Due to the high degree of complexity and continued need for more research, a Punnett Square is not an effective tool in analysing the heritability of ADHD

THE **7R** OF DRD4

DRD4[19]

The DRD4 gene is one of the most highly associated genes with ADHD. It is not known exactly how the polymorphism of DRD4 affects or increases ADHD suceptibility. DRD4 codes for the dopamine receptor D4. Dopamine receptors are activated by the neurotransmitter dopamine. Dopamine is a key component in the mesolymbic system which regulates emotions and behavior, particularly with the regards to reward response.

- Chromosome 11p 15.5
  - ~900 Genes
- 9 different alleles
- 2 - 10 repeats (2r, 3r, etc.)
- 4R = 65% of global population average
- 7R = 19% of global population average

7R Allele Distinct Associations[24]

- Developing ADHD and other psychological traits including addictions
- Thinning of prefrontal and posterial cortexes
- Highly associated with Novelty Seeking
- Seems to exist in high proportions in nomadic cultures
- 7R coded dopamine receptor appears to be less responsive to dopamine.
- Appears to have first mutated 40,0000 years ago
- Younger and more varied than the other alleles

Footnotes

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History Detail[3]

A Sir Alexander Crichton, a Scottish physician, travelled all across Europe in the 18th century studying mental illness. In 1798 he published three books from his observations including one chapter titled, "On Attention and Its Diseases" where he described patients with an "incapacity of attending with a necessary degree of constancy to any one object." Although his observations are by no means an exact parallel with the modern day criteria for ADHD, they provide evidence that ADHD could have existed in the 18th century3.

B Heinrich Hoffmann, a renowned German psychiatrist who rejected the sentiments of the day that mental illness patients were simply criminal, published a series of children's books that included characters such as "Fidgety-Phil" and "Johnny Look-In-the-Air" which many authors believe are early descriptions of ADHD and ADD.

C Sir George Frederic Still gives his historic Goulstonian Lectures a series of three lectures to the Royal College of Physicians of London where he describes *"a defect of moral control as a morbid manifestation, without general impairment of intellect and without physical disease."* Although his description does not fit the modern criteria for ADHD he made many observations that helped shape it.

D In the 1930s, by mere accident, it was discovered that some of these children, who were being hospitalized for "emotional problems" including hyperactivity, improved considerably when they were given a "headache" medication that turned out to be a brain stimulant. Although this would prove to be a fundamental key in the neurobiological origins of what these patients were likely suffering from, this discovery was more or less ignored for over twenty years. In the meantime the principle reigned true that behavioral disorders have no biological basis whatsoever. Unfortunately, this is still a common mis-assumption that is being actively fought against today.

E The hyperactive-child profile was accepted by the psychiatric community as a profile that was outside of the range of "normal" or "healthy" brain function and in 1968 "Hyperkinetic Reaction of Childhood" was included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) II. The affect of a brain stimulant on these children ruled out brain damage as the sole indicator, however the lack of any underlying biological indicator put a clear focus of future efforts to define the disorder on a child's defcits.

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G In 1970s it was suggested that a defficit of innattention was a more significant problem observed in school children, and in the 1980 version of the DSM, "Hyperkinetic Reaction of Childhood" was reconceptualized as "Attention Deficit Disorder with or without Hyperactivity" (ADD). This focus on specifc behavioral deficits would continue up to present day, enduring numerous alterations to diagnostic criteria, and the inclusions or exclusions of several peripheral symptoms.

H In 1990, Zametkin et al. found that children with ADHD had lower levels of cerebral glucose metabolism than in non-ADHD controls. This suggested that brain function was reduced in children with ADHD, indicated a neurological deficit.

I According to the most recent DSM-V (2013) the disorder is labeled "Attention Deficit/Hyperactivity-Impulsivity Disorder" (ADHD) with three subtypes; Primarily Innattentive, Primarily Hyperactive/Impulsive, and a Combination Type. ADHD in adults recognised for the first time in the DSM. There are still no biological or genetic indicators formally acccepted for diagnosis.