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# Genetic contributions to ADHD

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## Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental condition, affecting about 5% of children globally. Although considered a childhood condition, the symptoms and associated impairment can be life-long. In children, ADHD is more commonly diagnosed in males, but the sex ratio decreases in adults.[1] ADHD is associated with cognitive difficulties, especially executive functions (e.g., working memory, inhibitory control). ADHD commonly co-occurs with other neurodevelopmental conditions, including autism, motor coordination difficulties, and learning difficulties. Similarly to other neurodevelopmental conditions, ADHD is highly heritable.

The last decade of genetic research has seen significant breakthroughs in our understanding of the genetic contributions to ADHD and how these risks exert their effects in the population.

## Subject

Recent genetic studies have begun to identify robustly associated variants which increase ADHD risk. Another major advance has been studies examining the population-level impact of ADHD-linked genetic variants, including in clinical and general population samples.

**Problems**

One big hurdle to genetic discovery is not unique to ADHD; given the vastness and complexity of the human genome, genetic information from a large number (10,000s or even 100,000s) of individuals is needed to enable discovery. Another challenge is that ADHD is heterogeneous, meaning that people with ADHD differ in terms of their diagnostic subtype, symptom severity, symptom persistence, co-occurring conditions, and long-term outcomes.

**Research Context**

ADHD is associated with a significant negative impact on mental health (e.g., anxiety, depression, substance misuse), educational attainment, relationships, employment, and physical health. A better understanding of the genetic contributions and how they impact on heterogeneity is needed to inform clinical practice and improve outcomes for individuals with ADHD.

**Key Research Questions**

What are the specific genetic risk factors that increase risk for ADHD? What can explain the high levels of comorbidity between ADHD and other neurodevelopmental and psychiatric conditions? What is the impact of ADHD genetic risk at a population level? Can genetic factors help us better understand the heterogeneity in ADHD?

**Recent Research Results**

Given the high heritability of ADHD (estimated at about 76%),[2] numerous genome-wide association studies (GWAS) have sought to identify specific genetic variants contributing to ADHD risk. GWAS compare the population frequency of millions of genetic variants in individuals with and without ADHD, using a hypothesis-free approach. The first of these studies to succeed in identifying robustly associated markers, analysed data from 20,183 individuals with ADHD (primarily children) and 35,191 comparison individuals.[3] This GWAS identified 12 loci[a] consisting of common single nucleotide polymorphisms[b] that showed a different population frequency in individuals with and without ADHD. The study estimated that common variants collectively account for about 21.6% of ADHD risk, with further genetic markers to be identified. Indeed, a more recent study built on this work with the inclusion of genetic data from 38,691 individuals with ADHD and 186,843 comparison individuals,[4] identifying 27 genomic loci linked to ADHD. Both studies highlighted that ADHD is highly polygenic, with likely thousands of variants contributing to

ADHD risk. They also examined the expression of the implicated genes in a variety of cell types, tissues, and brain development stages, concluding that implicated variants were important for key neurological processes, including central nervous system tissue, embryonic brain development, and dopaminergic neurons.

Significant progress has also been made in identifying rare genetic variants linked to ADHD. These include copy number variants (CNVs)[c], which are large sections of chromosomes with fewer or more copies than usual (i.e., deletion or duplication), and rare single nucleotide exonic mutations that disrupt or alter protein formation. While large CNVs have been linked to ADHD for over a decade,[5] recent studies have linked specific CNV regions to ADHD (examples include deletions at 15q11.2 and 22q11.21 and duplications at 16p11.2 and 16p13.11).[6] Studies have also implicated rare exonic mutations[d],[7] as well as de novo (i.e., non-inherited) CNVs,8 but samples have been too small to identify specific risk variants within these classes of variation.

The large GWAS have contributed to our understanding of ADHD beyond discovery of specific risk factors. Studies indicate that there are high degrees of shared genetic risks between different definitions of ADHD (e.g., diagnosis and continuously assessed population traits,[3] male and female ADHD,[9] and childhood and adulthood diagnoses[10]). It is now also abundantly clear that ADHD genetic risks are shared with other neurodevelopmental conditions, notably autism,[7,11] and psychiatric disorders, notably depression.[12] ADHD also shares a substantial proportion of genetic risks with other disorders and traits, including type 2 diabetes, smoking behaviours, insomnia, and low educational attainment.[3] This widespread shared aetiology is likely to at least partly explain the co-occurrence of ADHD with these conditions and traits.

Another noteworthy contribution from GWAS analyses is that discoveries can be taken forward to examine the impact of ADHD genetic risk at a population level. Information from discovery GWAS can be used to calculate ‘polygenic risk scores’ (PRS) in an independent sample; these PRS indicate an individual’s genetic predisposition towards ADHD. For example, in the latest ADHD GWAS, PRS were derived in a clinical sample of children and adults who had undergone cognitive testing; ADHD PRS were associated with lower abilities in working memory, attention, and cognitive reasoning.[4] A systematic review of ADHD PRS studies found widespread evidence of association with population level traits, including in the domains of cognition, education, psychopathology, brain structure, physical health, and socioeconomic factors.[13]

One useful application of PRS includes examining the impact of genetic risks on heterogeneity within ADHD clinical samples. It is clear that genetic risks contribute to whether an individual will develop ADHD or not. A key question is whether genetic risk additionally impacts on severity, co-occurring conditions, and long-term outcomes in those diagnosed with ADHD. Indeed, higher ADHD PRS are associated with co-occurring conduct disorder,[14] substance use (e.g., alcohol and cannabis),[15] emotional dysregulation,[16,17] and executive function difficulties.[18,19] These studies suggest that the presence of specific co-occurring difficulties may be clinical markers of a greater genetic predisposition to ADHD in diagnosed individuals.

**Research Gaps**

Larger samples are needed for continued discovery of genetic contributions to ADHD. Additionally, analysis of genetically diverse samples is urgently needed. Existing studies primarily consist of individuals of European ancestry and genetic findings may differ across populations.[20] A limitation of existing PRS methods is that predictive ability is highly reduced in samples that do not match the ancestry of the discovery data used to calculate scores.[21] The inclusion of ancestrally diverse samples may also aid fine mapping to pinpoint the causal mechanisms of genomic regions linked to ADHD. With a rapidly growing number of implicated regions, much more work is needed to fully understand the impact of causal genetic factors on biological function. Further work is also needed to understand the environmental context for ADHD symptom onset and progression.

**Conclusions**

ADHD is a highly heritable, neurodevelopmental condition, with emerging discoveries implicating genetic variants that play a key role in brain development. It is the extreme end of a dimensional population trait, with genetic risks shared across sub-threshold symptoms and diagnosis. ADHD often persists into adulthood, with shared genetic factors between childhood and adulthood, as well as between males and females. Genetic risks are also shared with other conditions and related traits. This could explain the high level of co-occurrence with varied conditions such as autism, depression, and diabetes. Genetic risk factors may also help explain the clinical heterogeneity seen with regards to co-occurring neurodevelopmental and mental health outcomes in individuals with ADHD. Recent genetic studies provide a solid foundation for continued discovery and understanding of the aetiology of ADHD, with a view towards a precision medicine approach to support people impacted by ADHD.

## Implications for Parents, Services and Policy

The widespread evidence of high levels of shared genetic risk factors between ADHD and other conditions, has important implications. Firstly, when young people are experiencing mental health difficulties, they may benefit from parents and teachers considering whether these difficulties could indicate underlying neurodevelopmental difficulties such as ADHD. Similarly, clinicians working within child and adolescent mental health services should be aware of these strong biological links across different conditions. Given the lifelong consequences of ADHD, more resources are needed to decrease waiting lists for ADHD assessment and treatment, for educational support for those with ADHD, as well as for training of teachers and doctors to recognise ADHD and its heterogeneous presentation. Finally, given emerging evidence of ADHD-implicated genetic risk factors, future policies related to genetic testing and counselling could consider ADHD amongst other genetic conditions (such as autism and intellectual disability).

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**Notes:**

[a] **Locus (plural: loci):** The physical site or location of a specific gene on a chromosome.

[b] **Single nucleotide polymorphisms:** A small genetic variation in a human's DNA.

[c] **Copy number variants (CNVs):** Genes were thought to exist in 2 copies in our DNA. However, it is not always so. Some genes are sometimes present in 1, 3 or 4 copies in some individuals. This is what is called copy number variation.

[d] **Exonic mutations:** Exonic variants are the parts of genes which typically code for proteins. Mutations in these regions cause a genetic alteration in the DNA sequence and can impact on the proteins that are formed.