

HYPERACTIVITY AND INATTENTION (ADHD)

ADHD and Genetics

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Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood onset disorder that frequently persists into adulthood and is associated with the development of cognitive and functional deficits and comorbid disorders. The disorder tends to run in families and numerous twin studies find that ADHD is highly heritable, indicating the predominance of genetic influences in the aetiology of the disorder. While such studies do not exclude the importance of environmental factors they suggest that in most cases these interact with genetic factors; although exceptional environments such as severe early deprivation,¹ or exceptional genetic risk factors such as rare *copy number variants*² may exert large effects on disease risk in some cases. The nature of the genetic influences on ADHD is largely unknown although it is thought that this largely results from additive and interactive effects of common genetic variation.

Subject

Genetic studies of ADHD are relevant in two main ways. First, quantitative genetic studies enable the investigation of the extent of genetic effects on ADHD and the extent to which these are shared with associated cognitive impairments, brain function deficits and comorbid disorders and traits. Second, molecular genetic studies enable the identification of the specific risk factors involved, enabling a detailed understanding of the underlying molecular and neurobiological mechanisms involved.

Key Research Questions

What are the genetic influences on ADHD and the mechanisms that mediate genetic effects on behaviour?
How do genetic and environmental factors interact in the aetiology of ADHD and associated behavioural and cognitive traits?

Recent Research Results

Family and twin studies delineate a disorder that tends to run in families with a risk to first degree relatives in the order of five- to tenfold the population rate.^{3,4} The proportion of phenotypic variance explained by genetic factors (heritability) averages around 76%.⁵ The analysis of population twin and ADHD *proband-sibling* samples suggest that genetics influence levels of ADHD throughout the population and that ADHD is best perceived as the extreme of one or more continuously-distributed traits.³ The two symptom domains of ADHD ? inattention and hyperactivity-impulsivity ? share most but not all their genetic influences, suggesting that unique as well as common genetic and neurobiological processes are involved.⁶ Further studies have investigated the degree to which genetic influences are shared between ADHD and associated disorders and traits. These find that ADHD, particularly inattentive symptoms, share genetic influences with dyslexia;⁷ hyperactive-impulsive symptoms with oppositional problems;⁸ and ADHD with symptoms of autism spectrum disorder.⁹ These are thought to be *pleiotropic* effects of genes that are expressed in more than one clinical disorder.

More recently the overlap of familial effects on ADHD and cognitive performance deficits identified two familial cognitive factors.¹⁰ The larger factor, reflecting 85% of the familial variance of ADHD, captured all familial influences on mean reaction time and reaction time variability on a speeded reaction time task; while a second smaller factor, reflecting 12.5% of the familial variance of ADHD, captured all familial influences on omission errors and 60% on commission errors on a *go/no-go task*. Moreover, the cognitive factors were found to be independent of shared genetic effects between ADHD and IQ.¹¹ These two cognitive performance factors therefore seem to index most of the familial influences on ADHD and are thought to result primarily from genetic factors. As such, further work is now needed to delineate the genetic factors that underlie these two familial cognitive factors and the neurobiological processes involved, and to clarify whether these mediate the genetic effects on behaviour or whether they represent pleiotropic effects.

Molecular genetic studies on ADHD started with candidate gene association studies in the mid-1990s, with the first two reported associations between genetic variants in the *dopamine D4 receptor* (DRD4) and dopamine transporter (DAT1) genes. Subsequently, association was reported with a microsatellite marker near to the dopamine D5 receptor gene (DRD5). Since then there have been numerous replication studies with only a few independent replications, however meta-analysis of available data reported strong evidence for the association with DRD4 and DRD5 that reached genome-wide levels of significance in the study of Li and colleagues.¹² Evidence for the association with DAT1 has been far less consistent, with generally only weak evidence of association,¹² although there are several potential sources of heterogeneity that might account for this, including: specific association with ADHD that is not comorbid with conduct disorder,¹³ association with specific haplotypes (correlated sequences of correlated genetic variation),^{14,15} and the interaction with environmental measures such as maternal smoking during pregnancy.¹⁶⁻¹⁸ These candidate gene findings are important because they were the first direct evidence that genes regulating neurotransmission, particularly dopamine regulation, are involved directly in risk for ADHD; and confirmed a priori hypotheses derived from the immediate and marked effects of stimulants on ADHD symptoms that are thought to relate to the effects of stimulants on dopamine availability at neuronal synapses.

There have been numerous other candidate gene studies focusing mainly on the *dopamine, serotonin* and *noradrenalin* systems. These were recently reviewed by Gizer and colleagues¹⁹ who reported significant association following meta-analysis for several genes (DRD4, DAT1, DRD5, DBH, ADRA2A, 5HTT, TPH2, MAOA, and SNAP25). Previous research had estimated the overall impact of the most replicated gene findings

and found that around 3.3% of the variance was explained by the additive effects of these genes; accounting for only 4.3% of the estimated heritability of ADHD of 76%.²⁰ Additional work is clearly needed to explain the rest of the genetic influences on ADHD.

Further studies have taken advantage of *single nucleotide polymorphism (SNP) arrays* that enable genotyping of genetically informative markers across the entire human genome. Depending on the density of the arrays these may account for 80% or more of common genetic variation. In ADHD, genome-wide association studies (GWAS) have yet to establish confirmed novel associations, since no individual SNP has yet to reach genome-wide levels of significance. The problem is that conventional levels of significance in the region of .05 to .001 would be found by chance with SNPs throughout the genome, due the very large number independent haplotypes (correlated sequences of correlated genetic variation) across the genome. As a result, higher levels of significance, in the region of 5×10^{-8} , are recommended to adjust for the low prior odds of association.²¹ This has meant that for most common complex disorders, 12,000 or more samples are needed to reliably identify a few associated SNPs, since in nearly all cases only small genetic risks have been identified for specific risk *alleles* with odds ratios in the region of 1.1 – 1.4 or less. The first GWAS study of ADHD investigated 438,784 SNPs in 958 combined type ADHD proband-parent trios. No genes of moderate to large effect were identified²² and no findings passed genome-wide levels of significance. However, when a set of 51 candidate genes was investigated, there was significant group evidence for association from the selected SNPs, implicating mainly dopamine, noradrenalin and serotonin neurotransmitter genes. Similar findings were subsequently reported in a study that combined genome-wide association data from several studies.

Of particular interest is the Cadherin gene (CDH13), which has been found to be associated with ADHD in more than one GWAS study and lies within the only region that reached genome-wide significance in a meta-analysis of linkage studies of ADHD.²³⁻²⁵ This finding and other hints from GWAS indicate that genes involved in cell division, cell adhesion, neuronal migration and neuronal plasticity may also confer risk for ADHD.²⁶

Overall there is a long way to go to delineate the specific genetic factors that explain the high heritability of the disorder. This is, however, a common phenomenon in common disorders research and several potential explanations for the so called 'dark-matter' of heritability has been put forward. Potential reasons include numerous genes of very small effect, genetic heterogeneity with risk conferred by many different genes and variants within genes, higher order interactions between genes and with environment and aetiological heterogeneity. In addition, we do not yet understand the contribution made to ADHD from rare copy number variants (CNVs) or other types of rare genetic variation; although recent data suggest that in a few cases CNVs may be the main cause of the disorder.²

Finally, the focus of much of the genetic research has moved to the identification of intermediate phenotypes, measures of neurobiological function that mediate genetic effects on ADHD and may be more proximal to gene function. For example there is evidence from a few *fMRI* studies for greater effect sizes from specific genetic variants.^{27,28} Were this also to be the case for cognitive variables sharing genetic effects with ADHD it might be possible to identify genetic variants associated with ADHD following genetic investigations of the intermediate phenotypes. As mentioned genetic influences on ADHD appear to be indexed mainly by two familial cognitive factors measured by poor performance leading to slow and variable reaction times and an increase in commission and omission errors on cognitive performance tasks,¹⁰ so that intermediate phenotype could usefully focus on the processes that underlie these cognitive performance impairments in ADHD.

Interestingly, the most replicated genetic association with cognitive performance measures in ADHD is an inverse association between cognitive function and ADHD risk allele from DRD4. Among children with ADHD the high risk 7-repeat allele for ADHD is associated with less cognitive impairment than those carrying non-risk alleles.²⁹ This unexpected finding has also been found with the gene ZNF804A and schizophrenia,³⁰ suggesting that this may be a common finding in neuropsychiatric disorders. These findings suggest that cognitive performance may indicate important sources of heterogeneity with the cognitively less impaired group indicating a discrete molecular pathogenesis.

Research Gaps

Further work is needed to identify both common and rare genetic variants that account for the heritability of ADHD; using very large samples and future whole genome sequencing technologies. Neurobiological research needs to focus on measures that are genetically correlated with ADHD and use genetic association data to determine the nature of the cognitive, neuronal and cellular processes that mediate genetic risks on behaviour. Genetic studies of ADHD in adults are only just beginning, but it is expected that some genetic factors will influence risk for persistence and remission of the disorder during the transitional years from childhood to adulthood. Finally, further work is needed to identify environmental risks that act in an additive or interactive way with genetic risks for ADHD.

Conclusions

ADHD is a highly heritable disorder that starts in childhood and often persists into adulthood. Quantitative genetic studies help us to understand the aetiological links between ADHD and co-occurring disorders and traits; and the cognitive processes that mediate genetic effects on behaviour. Further work is needed to understand the processes that underlie the associated cognitive performance deficits such as reaction time and errors performance deficits. Dopamine system genes have been implicated in the aetiology of ADHD, particularly the DRD4 and DRD5 genes, and there is evidence from GWAS studies that other genes regulating neurotransmission and neurodevelopment, such as SNAP-25 and CDH13, are involved. Recent studies have identified rare copy number variants as a major risk for ADHD, but these only appear to affect a few cases. Further work is needed to explain the 'dark matter' of heritability which is yet to be explained by the genetic variants associated with ADHD to date.

Implications

Family, twin and adoption studies have had a major influence on the way that we perceive ADHD, and this in turn has influenced clinical decision making. We know that the disorder is largely inherited and that the genetic influences account for stability of ADHD over time. Furthermore genetic studies have helped our understanding of the development of comorbid disorders. Future work will use genetic data to identify aetiologically distinct subgroups with the aim of improving the prediction of clinical outcome and developing novel targeted intervention strategies to treat the disorder and prevent its progression into adulthood. These are critical strategies because of the very high personal and societal costs of ADHD, including education and employment problems, high accident rates and risk for the development of anxiety, depression, drug and alcohol addiction and antisocial behaviour.

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