The Genetics of ADHD

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Abstract

Results from family studies, adoption studies and, in particular, twin studies have indicated that there is a strong genetic predisposition to ADHD. However, environmental factors also appear to be important. No single gene is associated with a high risk of ADHD. Among the candidate genes that have been studied, the increased risk of ADHD associated with each gene is small; it is highest for the dopamine receptor gene DRD4 (odds ratio 1.33, 95%, confidence interval 1.15-1.54). Although genetic studies offer great promise and there have been significant advances in the technology, the translation of genetics research into clinical practice for the management of ADHD remains a challenge.

Introduction

Attention deficit hyperactivity disorder (ADHD), comprised of the triad of inattention, hyperactivity and impulsivity, is one of the most common childhood-onset neurodevelopmental disorders, with a prevalence of around 5% in children (1) and 3% in adults (2). While the onset is usually before the age of 7 years, a majority (up to 65% of cases) have persistent, impairing symptoms into adulthood (3) and therefore it is associated with significant academic, behavioural and social impairment throughout the life span (4,5). Consistent evidence for the importance of genetic factors in the aetiology of ADHD has come from both behavioural genetic studies and molecular genetic studies.

Behavioural genetic studies

Traditional behavioural genetic research, including family, twin and adoption designs have been used to examine if ADHD runs in families and how important genetic factors are in its expression.

Family studies evaluate the relative risk for other members of the family if one member of the family has been diagnosed with ADHD. These have consistently reported that parents and siblings of children with ADHD are 4-6 times more likely to have ADHD than the parents and siblings of children who do not have ADHD, the risk being even higher for those with persistent ADHD (6). However, traits and disorders can cluster in families because in addition to genes, they share much of their environment; twin and adoption studies are needed in addition to family studies to separate the effects of genes from common environment.

Adoption studies are difficult to carry out due to difficulty with accruing adequate numbers; however, there has been support for the importance of genetic factors in ADHD using this method in that adopted children with ADHD are more similar to their biological parents on ADHD measures, than to their adoptive parents (7).

Twin studies can be used to examine the presence or absence of a categorical diagnosis of ADHD (concordance or discordance) or the correlation between dimensional ratings of ADHD traits in monozygotic (MZ) and dizygotic (DZ). The higher the concordance/correlation in MZ twins (share ~100% of their genes) compared to DZ twins (share ~50% of their genes), the greater the genetic contribution and the higher the heritability (h 2) estimate. Concordance rates for ADHD have been found to be significantly higher for MZ than DZ and even recent, improved, systematic analyses taking into account possible biases of twin studies (such as lack of power to detect sibling interaction and the correction used for contrast effects), have estimated that genetic factors explained 60% of the phenotypic variance of ADHD (8). Furthermore, it appears that whether ADHD is defined categorically by diagnostic algorithms or dimensionally by rating scales the genetic component is strong and there is genetic overlap between these two constructs (9). Criticisms of twin studies have included the use

of the "equal environment assumption" (EEA) in mathematical modelling of the data in that the environment of MZ and DZ twins with ADHD may not be the same, however two studies of ADHD have demonstrated that biases introduced by possible violation of the EEA do not significantly affect the heritability estimates (10;11) and therefore twin studies can be interpreted reliably as supplying evidence for the importance of genetic factors in ADHD (8).

a) In addition to simply answering the question about the size of the genetic component of ADHD, behavioural genetic studies have been used to examine a variety of hypotheses e.g. (i) the homogeneity of DSM-IV subtypes of ADHD (combined, inattentive, hyperactive-impulsive), (ii) if the genetic component is different for males and females, or (iii) if there is an effect on co-morbidity.

b) Results to date provide conflicting evidence in favour of genetically distinct subtypes (12), although it is likely that while genes associated with the hyperactivity-impulsivity dimension will also be associated with the inattentive dimension, there is some support for some symptom-specific genes also (13).

c) Despite the higher prevalence of ADHD in males (~3:1) (1), twin studies have not shown a substantive quantitative or qualitative sex difference for ADHD combined subtype (14;15). However for the inattentive subtype, a second genetic factor has been described more commonly in girls that was not present in boys and may account for the genetic correlation between anxiety disorder and inattentive symptoms observed in girls and not boys (16;15;17). The lower overall prevalence of ADHD in girls might be explained by a higher liability threshold model and that girls may have some protective factor(s) (e.g. oestrogen) that is neuroprotective (18;19).

d) Comorbidity of ADHD with conduct disorder has been found to index a phenotype with a higher genetic load (6;20;21) and longitudinal twin data suggest that common genetic factors substantially underlie the comorbidity of ADHD with conduct disorder (15). ADHD also co-occurs with reading disability and autism spectrum disorders (ASDs). Most studies show a stronger genetic overlap between reading disability and inattentive problems rather than with hyperactive/impulsive symptoms (22). Likewise, evidence suggests that shared genetic risk factors are responsible for the co-occurrence of ADHD with ASD (23;24).

Molecular Genetic Studies

Since the 1990s, candidate gene association studies of ADHD have been carried out. These studies test if there is a statistical difference between the presence of a genetic variant in people with ADHD compared to unaffected controls. These studies are based on *a priori* hypotheses and have focussed on common genetic variation (>/=5% of population) in a limited number of genes (mainly involved in neurotransmitter pathways) that have been implicated in the aetiology of ADHD.

A meta-analysis of candidate association studies reported significant associations between ADHD and common variants in the following 6 genes; dopamine transporter (DAT1 or SLC6A3), dopamine receptor 4 (DRD4), dopamine receptor 5 (DRD5), serotonin transporter (5HTT), serotonin receptor 1B (HTR1B), and synaptosomal-associated protein 25 (SNAP25) (25). The odds ratio for each of these genes individually was very small, the highest being for DRD4 at 1.33 (CI 95% 1.15-1.54). It is likely that multiple risk genes of small effect combine additively, interactively or with the environment to produce ADHD symptoms (26) . Structural and functional brain imaging studies have lent further support for the aetiological importance of some of these implicated genes (e.g. SLC6A5 and DRD4) (8).

A whole genome systematic approach has been to look for genetic linkage in families with multiple affected individuals (usually affected sibling pairs) and aim to identify broad regions in the genome that could harbour susceptibility genes. This approach is based on the premise that if there is a risk variant in a region of the genome, there will be a region of the chromosome extending for some distance beyond it that will be shared more often than expected by siblings who are both affected compared to siblings where one is unaffected. A meta-analysis of seven independent linkage scans in ADHD has identified genome-wide significant linkage on chromosome 16 between 64 and 83 Mb

in which lies the CDH13 gene, which has been implicated in substance use disorders (27). However, it has been difficult for individual groups to achieve independent replication of linkage findings. The reasons for this may be that large enough numbers have not been achieved, that the common susceptibility genes for ADHD are of small effect size and that this approach is not most suited to finding risk genes for ADHD (28).

More recently, with the progress that has been made through the Human Genome Project and improved technologies, a number of genome-wide association studies (GWASs) also known as whole genome association study (WGA study or WGAS), have been carried out for ADHD. This method systematically examines genetic variation in most/all genes across the entire genome in a single experiment using a glass microarray. In order to have enough power to detect signal it is important to have large sample sizes of cases and controls. This has been a problem for ADHD, as a meta-analysis of all published studies to date revealed that despite the emergence of several novel genes for ADHD using this method, the combined total of all samples collected to date from around the world is still underpowered (29). Other psychiatric disorders with similarly complex genetic architectures to ADHD have been successful, but only with sample sizes of tens of thousands of cases. However, the data from GWAS studies has been useful in that it is possible to pull out genes that rank highly in terms of significance (even if not reaching a stringent genome-wide significance of $p=10^{-8}$) and use these in bioinformatic pathway analyses to determine which neural pathways may be disrupted in ADHD. Approximately half of the proteins coded for by the ~100 highly ranked genes so far, are involved in neurite outgrowth (neurotrophins) and point towards the importance of the antenatal period of brain development for ADHD (30).

In addition to common genetic risk variants, there are rare family/individual-specific genetic variants that can affect genes involved in neurodevelopment. A class of rare variants that have recently aroused interest are referred to as copy number variants (CNVs). These are segments of DNA of at least 1kb (but can be much larger) that vary in number between individuals. Copies of these segments can be increased from the normal two copies (duplications or insertions, where there are three or more copies) or decreased (deletions, where there is one copy). Recent studies of autism, schizophrenia, epilepsy and intellectual disability have implicated these CNVs as being potentially pathogenic (31). CNVs are part of normal variation in the human genome and not all of them are thought to be pathogenic (32). Even those that are putatively pathogenic have variable penetrance (33). Advances in technology (e.g. array CGH is offered now by many cytogenetics laboratories) have made CNV detection more cost and time effective. There have been few studies of CNVs in ADHD to date. An initial study did not report an excess of duplications or deletions in ADHD compared to controls; however, the CNVs found in the ADHD sample were significantly enriched for genes reported as candidates in other neuropsychiatric disorders and neurodevelopmental pathways (34). A second study in a sample with severely affected individuals with ADHD and controls found an excess of putatively pathogenic CNVs in the ADHD sample (35). This study reported a duplication of a chromosomal region that includes the gene encoding neuropeptide Y (NPY) and this was associated with increased NPY plasma concentrations, and impairments on functional neuro-imaging tasks related to reward and emotion processing. Finally, a third study reported an increased rate of CNVs in ADHD compared to controls (0·156 vs 0·075), especially in individuals with intellectual disability (ID), though there was also a significant excess in cases without ID (36). CNVs identified this ADHD cohort were significantly enriched for loci previously reported in both autism and schizophrenia, suggesting pleiotropy (when a single gene can influence multiple traits).

Other rare genetic phenomena comprised of a number of different chromosomal anomalies including abnormalities in the number of chromosomes (aneuploidies) and single gene disorders have been recognised for many years to be associated with higher rates of ADHD (37). Fragile X syndrome, tuberous sclerosis and several microdeletion syndromes including Smith Magenis and Velocardiofacial (VCFS; 22q11 microdeletion) syndromes are associated with ADHD. Again these abnormalities are also associated with other neuropsychiatric disorders (e.g. autism spectrum disorders and psychoses).

In summary, several lines of converging evidence support a strong genetic component in the aetiology of ADHD. However, this does not negate the importance of environmental factors. Genetic

risk and environmental factors can affect ADHD through gene-environment correlation or gene-environment interaction (see Stergiakouli and Thapar (28) for review). It is not easy to identify or measure environmental risk; however, although several factors have been individually investigated for a link to ADHD, the best evidence to date relates to relatively rare extreme adversities such as extreme prematurity, very low birth weight, foetal alcohol syndrome and a pattern of behaviours associated with institutional deprivation in the early years (38). Molecular genetics is seen as an important tool with which to unravel gene-environment interplay in ADHD and early findings suggest that this line of enquiry promises to yield important insights in the future (39) .

Molecular genetic approaches have recently been used to identify genetic contributors to clinical response to pharmacological agents as well as to adverse drug reactions (ADRs), in the rapidly advancing field of pharmacogenomics (often used interchangeably with pharmacogenetics). This approach is particularly important for paediatric cases as there is significant inter-individual variability between young people in the clinical response (i.e. improvement of symptoms, dose-response relationship, and occurrence of side effects and adverse events) to the same pharmacological agent and furthermore the same child may respond to the same agent in different ways through time, because the affinity, functional capacity, and expression of the targets (e.g. enzymes and transporters) of medications vary along development (40) . Pharmacogenomic studies in ADHD have typically taken variants in candidate genes found to be associated with ADHD and examined clinical response to methylphenidate (31 studies) or atomoxetine (2 studies) (41), though systematic GWAS approaches are being undertaken (42) . There are some interesting initial findings relating to pharmacodynamic variants and methylphenidate response as well as pharmacokinetic variants (in the cytochrome P450 system, CYP2D6) and atomoxetine response and adverse events. This approach could have enormous clinical relevance in the short to medium term.

Translation of genetic studies into clinical practice will be a major focus of future research investment. Identifying specific genetic risk factors will improve diagnosis and classification as well as stratify patient groups for specific treatments. It is likely that the clinical genetics laboratories will universally substitute routine comparative genome hybridisation array technology (array CGH) for light microscopy and therefore increase the yield of detected structural genetic variants in neurodevelopmental disorders such as ADHD (43). Personalised medicine will be the goal of modern practitioners. Rapid advances in stem cell technology, specifically induced pluripotent stem cell (iPSC) technology, where an individual's somatic cells (e.g. blood, hair, skin cells) can be grown in a dish, transformed into stem cells and differentiated along neuronal lines and tested using several different drugs, could significantly advance the process of finding individualised therapies (44) .

GP Comment.

What have I learned from this paper?

1. ADHD has a tendency to run in families.

2. Because of this I shall be very aware of the possibility of the same diagnosis in other family members of a patient with ADHD.

3. Although there is a genetic predisposition to ADHD, no single gene has been identified as being responsible for the condition.

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