

Fitting the pieces together: current research on the genetic basis of attention-deficit/hyperactivity disorder (ADHD)

Evangelia Stergiakouli
Anita Thapar

Department of Psychological
Medicine and Neurology, MRC Centre
for Neuropsychiatric Genetics and
Genomics, School of Medicine, Cardiff
University, United Kingdom

Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a highly disruptive childhood-onset disorder that often persists into adolescence and adulthood. Comorbidity with other problems, such as autism, dyslexia and conduct disorder (CD) is very common. Although little is known about the pathophysiology of ADHD, family, twin and adoption studies have shown that it is highly heritable. Whole genome linkage studies suggest there are no common susceptibility genes of moderate effect size. Most published research has been based on functional candidate gene studies. The most consistent evidence for association with ADHD relates to a dopamine D4 receptor (*DRD4*) gene variable number tandem repeat (VNTR), a dopamine D5 receptor (*DRD5*) gene microsatellite and a dopamine transporter (*DAT1*) gene VNTR. In addition, the catechol-O-methyltransferase (*COMT*) val158/108 met variant has been shown to increase risk for associated antisocial behavior. The first genome-wide association studies (GWAS) of ADHD have been completed and although larger studies are still required to detect common risk variants, novel risk pathways are being suggested for ADHD. Further research on the contribution of rare variants, larger genome-wide association and sequencing studies and ADHD phenotype refinement is now needed.

Keywords: attention-deficit/hyperactivity disorder (ADHD), genetics, molecular genetics, genome-wide association study (GWAS), gene-environment interplay

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood-onset psychiatric disorders affecting 1.4%–6% of school children. The core clinical features are severe impulsiveness, lack of concentration and motor hyperactivity that result in impaired functioning in more than one setting (eg, home and school). This pattern of symptoms puts children at risk of education failure and disrupts family, teacher and peer relationships. ADHD is often accompanied by other psychiatric disorders and learning difficulties, notably oppositional defiant disorder (ODD), conduct disorder (CD), autism and dyslexia. ADHD is highly heritable and the investigation of genetic factors that increase risk can help elucidate its pathophysiology. The first part of this review discusses evidence on the genetic contribution to ADHD as well as specific clinical aspects, while the second part deals with molecular genetics studies.

ADHD phenotype and diagnosis

The use of internationally accepted diagnostic criteria has increased diagnostic reliability resulting in ADHD being one of the best-validated clinical diagnoses.¹

Correspondence: Evangelia Stergiakouli
Department of Psychological Medicine
and Neurology, MRC Centre for
Neuropsychiatric Genetics and Genomics,
School of Medicine, Cardiff University,
Henry Wellcome Building, Heath Park,
CF14 4XN Cardiff, United Kingdom
Tel +44 029 20687069
Fax +44 029 20687068
Email stergiakouliE@cardiff.ac.uk

There are two sets of diagnostic criteria used to define ADHD: the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) and the *International Classification of Diseases*, tenth edition (ICD-10; Hyperkinetic Disorder). The diagnosis of ADHD is based on reported symptoms. Most genetic studies have utilized standardized diagnostic criteria, although some have considered ADHD to be continuously distributed and assessed total ADHD symptom scores.

There is consistent evidence that ADHD is familial. Family studies of ADHD have reported increased rates of ADHD among parents and siblings of children with ADHD compared with relatives of unaffected controls. The relative risk in first degree relatives is considered to be between 4 and 5.4.¹ It is interesting that half siblings of children with ADHD have a lower risk of developing the disorder than full siblings, further highlighting the important role of inherited factors in ADHD.²

Adoption studies are able to disentangle the contribution of inherited and environmental factors. Five adoption studies have shown that the risk of ADHD is greater in biologically related relatives of affected individuals than in those who are unrelated and this provides strong evidence for a genetic contribution to ADHD.^{3,4}

Twin studies examine the contribution of inherited factors by examining the extent of disease concordance in genetically identical (monozygotic) and nonidentical (dizygotic) twin pairs. Many of these studies have focused on ADHD symptom scores, since a large-scale twin study has found that ADHD may be better viewed as the extreme end of a continuum rather than as a category.⁵ Such studies have all shown that ADHD is highly heritable and that 60%–90% of phenotypic variance can be explained by inherited factors.^{1,6} These high heritability estimates are comparable to those found for other neurodevelopmental disorders such as autism and schizophrenia. It is striking that heritability estimates are not 100%, meaning that there must be additional contribution from nonshared environmental factors, epigenetic and stochastic (random) effects or measurement inaccuracies. Epigenetic effects are heritable but reversible genetic changes that are not attributable to DNA sequence variation. They have been hypothesized to mediate the effects of environmental risks on psychiatric disorders.⁷

Twin studies have highlighted important issues about the measurement of ADHD as clinical information is usually gathered from different informants. ADHD scores derived from mother's reports have been found to be highly heritable with heritability estimates of 60%–91%.⁸ ADHD scores from

teacher reports are also heritable. It seems that the most reliable and heritable phenotype is achieved when combining both parent and teacher reports.⁹ Although using both parent and teacher reports appears to be the best option for defining child ADHD, self reports need to be considered when investigating adolescent and adult ADHD. Adolescents and adults with ADHD have similar patterns of psychiatric comorbidity and neurocognitive deficits to children with ADHD, although inattention is more prominent than hyperactivity-impulsiveness.¹⁰ According to twin studies, the heritability of ADHD symptoms derived by self reported ADHD scores in adolescents and adults is much lower than for ADHD symptoms derived from parent and teacher reports of child ADHD scores. Nonshared environmental factors, including measurement errors have been thought to explain the low heritability.

In summary, there is abundant evidence of a strong genetic contribution to ADHD. However, the influence of noninherited factors is also important. The evidence supports the use of both parent and teacher reports for defining ADHD in children. For adolescents and adults, where this is not feasible, self reports should be treated with caution when no other informant (such as a partner) is available.

ADHD subtypes

The DSM-IV-TR recognizes three ADHD subtypes. The combined type is diagnosed when six or more symptoms from each of two symptom categories (inattentive and hyperactive-impulsive) are present, while the inattentive or hyperactive-impulsive type is diagnosed when six or more symptoms from only one of the two categories are present. However, it is difficult to assess whether these subtypes are genetically distinct. The picture from family studies is not clear, although a meta-analysis suggested that there is overlap in terms of shared familial factors and only a small familial effect on subtype distinction.¹¹ Twin studies have also found shared genetic liability¹² although findings are not entirely consistent as other studies report distinct genetic and environmental contributions to the subtypes.⁹ In summary, although ADHD subtypes are recognized for diagnostic purposes, the evidence for distinct risk factors operating on different ADHD subtypes is not consistent.

Developmental course

At least half of those with childhood ADHD will still meet full diagnostic criteria in adolescence.¹³ The levels of overactivity and impulsiveness tend to decrease, while inattentiveness is more persistent. During adolescence

the problems of antisocial behaviour and substance abuse also emerge. Longitudinal studies have shown that ADHD symptoms and comorbid antisocial behavior also tend to persist into adulthood.¹⁴ Twin studies find that there are genetic influences not only on ADHD but also on its continuity. Most of the continuity in ADHD symptoms is attributable to genetic influences.¹⁵ There is also the suggestion that a persistent diagnosis of ADHD is associated with stronger family history.¹ Interestingly, despite diagnostic continuity over time, there are also reports of distinct genetic factors contributing to child and adult ADHD.¹⁶ In summary, ADHD is a persistent disorder with genetic factors contributing to its origins and persistence.

Comorbidity

Comorbidity is common and around two thirds of children with ADHD have a diagnosis of another psychiatric disorder. It is increasingly recognized that autism and other pervasive developmental disorders (PDD), which are also neurodevelopmental in origin, often co-exist with ADHD. Common characteristics of neurodevelopmental disorders include a tendency to more commonly affect males^{17,18} and having an onset in childhood. It has been suggested that there might be a set of common risk factors affecting brain development during critical stages that lead to such disorders. Twin studies indeed do find that ADHD and autism symptoms are influenced by a shared inherited risk.^{19,20} Further genetic or environmental factors may then be responsible for the manifestation of symptoms leading to diagnoses of specific disorders. It is striking that children with PDD are currently excluded from having a diagnosis of ADHD according to DSM-IV criteria, although they could benefit from treatment for their ADHD symptoms. They are also excluded from many research studies of ADHD despite the fact that they could represent one extreme of the distribution of neurodevelopmental disorders. The same is also true for children with ADHD and intellectual disability/mental retardation (IQ < 70).

The commonest comorbid disorders are CD and ODD. Their prevalence in children with ADHD ranges from 20%–40% and they increase the risk of poor outcomes in children with ADHD. It has been considered that the group of children with ADHD and childhood-onset CD is distinct from the groups of children with ADHD or CD only. In this comorbid group of children, ADHD is more severe and shows greater persistence in adult life.²¹ Family history is also stronger¹ and the presence of CD indicates higher genetic loading in ADHD.²² Early onset CD also represents a risk factor for poor outcome for children with ADHD.²³

To conclude, ADHD can co-exist with a wide range of psychiatric disorders and this could be due to shared inherited factors. The presence of CD appears to be an index of heterogeneity.

Sex differences

There are higher rates of ADHD in males compared with females. The male to female ratio in population cohorts is approximately 4:1.¹⁸ However, sex difference ratios are larger in clinical samples (7–8:1) than population cohorts due to referral biases, since boys with ADHD tend to be more disruptive than girls, making them more likely to be referred.²⁴ The phenotype of the disorder also differs between the two sexes. Boys tend to be more hyperactive, while girls are usually more inattentive.¹⁸ Research on the factors contributing to sex differences in ADHD has been limited. One possibility is that different genetic factors operate for males and females, although family studies show that ADHD in both sexes is familial and twin studies do not find major differences in the magnitude of genetic influences on ADHD in males and females.²⁵

In summary, sex differences in the prevalence and clinical presentation of ADHD are well-established but more research is required to explain these.

The contribution of gene-environment interplay in ADHD

It is well-recognized that psychiatric disorders, like other complex diseases, are influenced by both genetic and environmental factors.²⁶ Gene-environment interplay encompasses both gene-environment correlation and gene-environment interaction.

Several environmental factors have been considered in relation to ADHD, including low birth weight, prematurity, prenatal maternal smoking, alcohol consumption, maternal stress, psychosocial adversity and poor maternal diet, and toxins during the prenatal or neonatal period.²⁷ It is notable that the common characteristic of these environmental risks is that exposure is required during a critical period. For this reason it has been suggested that they might result in epigenetic (noninherited genomic) processes being triggered during a developmental window.⁷

Gene-environment correlation

Gene-environment correlation applies when exposure to a certain environmental factor depends on the genetic make-up of the individual or their parents. This means that genes could increase the risk of developing ADHD

by influencing exposure to certain environmental factors. In gene-environment correlation the risk effects of genes and environment are not distinct and genes may indirectly increase risk to ADHD by influencing exposure to risk and protective factors. For example, maternal smoking and stress in pregnancy have both been linked to ADHD. However there is evidence to suggest that these environmental risks are influenced by maternally-provided inherited factors²⁸ and index inherited liability to ADHD.

Gene-environment interaction

Gene-environment interaction is used to describe the phenomenon whereby a genetic factor exerts its effect when the individual is exposed to environmental risk.²⁹ Twin or adoption studies of ADHD on this topic have not been published, although this could indicate a publication bias against negative results.²⁹ Investigating gene-environment interaction in ADHD for specific gene variants is still at an early stage and there is a lack of robust replication studies. These results will be discussed later.

To conclude, most of the environmental factors that are considered to increase susceptibility to ADHD are prenatal risks. However, some studies highlight that risk factors associated with a disorder are not necessarily causal.²⁶

Molecular genetics of ADHD

Psychiatric disorders, including ADHD, are categorized as complex disorders; this means that, they are the result of multiple gene co-action, gene-gene and gene-environment co-actions and interactions. The process of identifying complex disorder susceptibility genes has so far mainly been based on examining common variation in the DNA of different individuals without necessarily being pathogenic (for more information see Thapar and Stergiakouli³⁰). This variation provides genetic markers/polymorphisms, such as single nucleotide polymorphisms (SNPs). Advances in technology have made mass genotyping of large numbers of SNPs for very big samples possible and more economical. The main three methods that have been used to identify common, susceptibility gene variants are:

- whole genome linkage studies
- candidate gene association studies
- genome-wide association studies (GWAS).

Whole genome linkage studies

Whole genome linkage studies are based on families with multiple affected individuals, mainly affected sibling pairs, and aim to identify broad regions in the genome that could

harbor susceptibility genes. The principle is that, if an allelic marker is linked to a susceptibility locus, affected relatives will share this allele more commonly than expected. Whole genome linkage studies of ADHD have been published and a meta-analysis of seven independent linkage scans yielded a significant association for 16q23 ($P^{SR} = 0.00034$, $P^{OR} = 0.04$). Interestingly, the same region came to light from a GWAS of quantitative traits related to ADHD. This region harbors the *CDH13* gene which has been implicated in substance use disorders.³¹

In summary, whole genome linkage studies have not been able to achieve replication or point unequivocally to regions harboring susceptibility genes for ADHD. This probably reflects the fact that there are no common susceptibility genes of large effect sizes for ADHD and whole genome linkage studies are not the most appropriate approach for identifying genes of smaller effect sizes.

Candidate gene association studies

Candidate gene association studies select genes that are hypothesized to be implicated in a disorder and then compare the frequencies of marker alleles in affected individuals (cases) and healthy individuals (controls). Genes are selected on the basis of findings from whole genome linkage, animal, pharmacological or imaging studies. However, these studies are based on assumptions about the pathophysiology of the disorder and since this is largely unknown in psychiatric disorders, they have not been very successful.

Genes within the dopaminergic pathway have been hypothesized to be implicated in the pathophysiology of ADHD due to the therapeutic effects of stimulant medication, which reduces ADHD symptoms by inhibiting the reuptake of dopamine.³² Animal studies also show that the dopamine transporter (*DAT1*) knockout mouse model (where the *DAT1* gene has been turned off to study the effects on the phenotype) exhibits hyperactivity and deficits in inhibitory behavior³³ and imaging studies of patients with ADHD provide evidence of changes in brain regions where dopaminergic systems are more active.³⁴ Genes on the dopaminergic pathway that have been investigated in relation to ADHD include dopamine D4 receptor gene (*DRD4*), dopamine D5 receptor gene (*DRD5*), *DAT1* and catechol-O-methyltransferase (*COMT*). Other genes notably serotonergic genes and synaptosome-associated proteins (SNAP-25) have also been studied.³⁵ According to a recent meta-analysis there is evidence that the serotonin transporter gene and the serotonin 1B receptor gene might be associated with ADHD.³⁶ However, since candidate gene association findings are not the focus of this

review, we will only discuss consistently replicated findings from meta-analyses or pooled analyses.

DRD4

The best studied *DRD4* gene polymorphism is a variable number tandem repeat (VNTR) in exon III of the gene. The number of repeats ranges from 2–11 and the 7-repeat allele reduces the ability of the receptor to bind dopamine according to *in vitro* studies. A significant association of the 7-repeat allele and ADHD has been reported in four different meta-analyses and pooled studies.^{1,36–38} The most recent meta-analysis by Gizer et al³⁶ reported a significant, modest association between ADHD and the 7-repeat allele ($P < 0.00001$, OR=1.27, 95% confidence interval [CI]: 1.16–1.39), although the authors also showed evidence of substantial heterogeneity in effect sizes across different studies.³⁶ Two studies have also suggested that the 7-repeat allele is associated with ADHD symptom persistence^{39,40} although findings are not entirely consistent.⁴¹

DRD5 gene

Another dopaminergic gene, the *DRD5* has been investigated in relation to ADHD and the 148-bp allele of a microsatellite at the 5' end of the gene was found to be significantly associated with ADHD in four meta-analytic studies.^{36,42–44} The most recent meta-analysis reported a significant association ($P = 0.000095$, OR = 1.22, 95% CI: 1.10–1.36) with moderate heterogeneity in reported effect sizes.³⁶ Although these results are very promising, the associated polymorphism is not located in the protein coding region of the gene and has no known function; it could be that this polymorphism is co-inherited with another polymorphism that is functional or that it influences gene function in a yet unknown fashion.

Solute carrier family 6A, member 3 (*SLC6A3* or *DAT1*)

A VNTR polymorphism in the three-prime-untranslated region (3' UTR) of the *DAT1* gene has been extensively investigated and a significant association between the 480-bp allele and ADHD ($P = 0.002$, OR = 1.1, 95% CI: 1.03–1.17) was found in an updated meta-analysis by Gizer et al.³⁶ The same meta-analysis found significant associations with other polymorphisms in the *DAT1* gene and substantial heterogeneity across studies. Significant association of the 480-bp allele and ADHD has also been reported in five previous meta-analyses and pooled analyses.^{1,38,44–46} The International Multicenter

ADHD Gene (IMAGE) project, a study of 776 ADHD cases that is the largest study to date, also reported a significant association but with a different polymorphism in the *DAT1* gene.⁴⁷ Although the data indicates that *DAT1* is a strong candidate gene for ADHD, most of the meta-analyses have found evidence of sample heterogeneity suggesting a very small effect size of this variant or the presence of multiple polymorphisms within the *DAT1* gene increasing risk to ADHD. The *DAT1* 148-bp allele has been reported as increasing sensitivity to the risk effects of maternal smoking during pregnancy.⁴⁸ Another study also found evidence of gene-environment interaction but with a different *DAT1* allele.⁴⁹ In contrast, there have been two negative reports of gene-environment interaction in relation to maternal smoking in pregnancy and *DAT1*.^{50,51} A further concern is that maternal smoking in pregnancy might not be a causal environmental risk but rather indexing inherited liability to ADHD.²⁸ Prenatal exposure to alcohol was also investigated in ADHD and it was found that it increased ADHD symptoms when a specific haplotype of SNP alleles in *DAT1* was present.⁵⁰ Two markers in the same gene, *DAT1*, have also been reported to interact with psychosocial adversity (defined by measures of family and parental adversity) and increase ADHD symptoms.⁵²

COMT association with CD symptoms in patients with ADHD

The most studied polymorphism in *COMT* is a functional SNP resulting in a valine to methionine substitution (val158/108 met variant). However, two pooled analyses^{1,53} and a meta-analysis³⁶ have found no evidence of association between this variant and ADHD. Interestingly, the *COMT* val allele yielded an almost significant result for males in the Cheuk and Wong meta-analysis.⁵³ Thus, it could potentially be involved in male susceptibility to ADHD.⁵³

There is however consistent evidence that the *COMT* val/val genotype is associated with CD symptoms in those with ADHD.⁵⁴ Since the first report, the same genotype was subsequently found to be associated with antisocial behavior in those with ADHD (but not in those without ADHD) in two independent populations from United Kingdom and New Zealand birth cohorts.⁵⁵ A pooled analysis of four studies also showed significant association with the val/val genotype.⁵⁵ The same genotype was also associated with increased aggressive CD symptoms in patients with ADHD.⁵⁶ These results suggest that some gene variants operate by modifying the ADHD phenotype rather than by increasing risk of disorder itself.

To summarize, the most robust evidence is for an association between the *DRD4* VNTR, the *DRD5* microsatellite marker, the *DAT1* 480-bp VNTR and ADHD. It is still unclear whether the *DRD4* VNTR is causal. The *DRD5* 148-bp microsatellite is 18.5 kb away from the gene but that does not mean it does not influence *DRD5* in a yet unknown fashion. As for *DAT1*, there is significant evidence of heterogeneity across studies, although it initially appeared as the strongest candidate gene. The evidence that the *COMT* val/val genotype has a modifying effect on antisocial behavior in ADHD is a consistent finding in the field of ADHD, since it has been replicated in multiple independent samples. At present there is no convincing evidence of gene-environment interaction in relation to ADHD.

GWAS

GWAS are currently regarded by many as the most promising method for systematically searching for complex disorder susceptibility genes. They involve testing several thousand or millions of SNPs across the genome without an *a priori* hypothesis, and it is believed that they will also be able to pick up genes of small effect. A major limitation is that they require extremely large sample sizes to overcome the problem of multiple testing and to avoid false-positive results that are simply the product of chance. Genome-wide association findings have been published for schizophrenia,^{57–59} bipolar disorder,⁶⁰ autism⁶¹ and other psychiatric disorders. For a review of GWAS on ADHD see Franke et al.⁶²

GWAS of ADHD have been undertaken but research is at a much earlier stage than for most other psychiatric disorders. The first such study used a sample of 959 family trios collected as part of the IMAGE I study⁶³ with 600,000 genotyped SNPs.⁶³ Although, none of the associated SNPs reached genome-wide significance, these results do not exclude the existence of genes that increase risk for ADHD. In a list of the top-25 SNPs, there were some interesting candidate genes for ADHD, including cannabinoid receptor 1 (*CNRI*).³¹ This gene is located in a region that is possibly associated with ADHD according to a recent meta-analysis of linkage studies⁶⁴ and it has been also associated with alcohol and drug abuse⁶⁵ but such findings require replication in a different ADHD sample. Results from the same genome-wide scan were used to test for association with quantitative phenotypes generated from the ADHD symptoms.⁶⁵ The authors tested three quantitative phenotypes (number of hyperactive-impulsive symptoms, number of inattentive symptoms and total number of symptoms) under three different genetic models, which increased the multiple testing burden. There were

two genome-wide significant results; one of them was an intronic SNP in Cadherin 13 (*CDH13*) associated with the total number of ADHD symptoms⁶⁶ and the other one was an intronic SNP in glucose-fructose oxidoreductase-domain containing 1 (*GFOD1*) associated with the number of inattentive symptoms. *CDH13* has been previously reported to be associated with substance abuse⁶³ and was on the list of the top-25 SNPs from the previous GWAS,⁶⁵ although the two studies are not independent.

Based on a list of candidate genes for ADHD compiled *a priori*, SNPs within Sodium/hydrogen exchanger 9 (*SLC9A9*), as well as other genes previously associated with ADHD, were associated with the disorder, although they failed to reach genome-wide significance.⁶⁷ Apart from being the top hit, *SLC9A9* also contained the largest number of associations in terms of SNPs and phenotypes. However, it was also the largest gene in this study.

A pooled GWAS not associated with IMAGE I analyzed 343 adult patients with persistent ADHD and 304 controls from Germany.⁶⁷ Although again there were no genome-wide significant findings, a large proportion of the top-ranked SNPs were located in genes expressed in the brain and some of them, have also shown association with substance abuse disorders, which are found very frequently in adult ADHD patients.³¹

In terms of overlap of GWAS findings in ADHD, *CDH13* on chromosome 16q24.2–24.3 stands out. This gene is further supported by the fact that it falls into the only significant linkage region from the meta-analysis by Zhou et al.⁶⁶ Although *CDH13* is not a classic candidate gene for ADHD, it codes for a cell-cell adhesion protein and is also a regulator of neural cell growth. Other interesting findings in the top-ranked results of these GWAS relate to Toll-like (*TLL*) genes.⁶⁸ They code for metalloproteases that cleave collagen and they are expressed in the brain. These findings highlight the fact that GWAS can point to novel risk pathways that would not be otherwise explored. However, caution is required given that no findings have achieved genome-wide significance levels or yet been replicated.

The IMAGE dataset was also used to perform a GWAS on ADHD with comorbid CD,⁵⁴ which as discussed earlier is considered to index heterogeneity.⁶⁸ There were no reported genome-wide significant associations, although 54 markers were nominally associated. However, the authors point out that their analysis was exploratory and any associations would require replication.⁶⁹

In summary the first findings from GWAS on ADHD have provided some interesting genes to explore while failing to

provide support for previous candidate genes and achieve any genome-wide significant results (Table 1). As GWAS of other complex disorders have shown,⁷⁰ the effect sizes of common variants are very small and this in practice means that success will only be possible if sample sizes are greatly increased. Collaborative efforts can help achieve the number of patients and healthy controls needed to have sufficient power to detect such small effects.

Other potential reasons for the limited success of ADHD GWAS are sample heterogeneity, and the fact inherited factors other than common variants could increase risk for complex disorders. Although rare variants are found in a small proportion of the population (usually less than 5%), their effect sizes can be far greater than those for common variants, since they are more likely to have important implications for gene function than common variants (Table 1).

Copy number variants (CNVs)

One category of rare variants includes CNVs, which are DNA segments, of at least 1 kb in size, that vary in number when genomes of different individuals are compared. They can be copy number gains (called insertions or duplications), when there is a relative gain of a DNA segment compared to the control genome, or they can be copy number losses (called deletions), when there is a relative loss of a DNA segment. The presence of a CNV in an individual does not necessarily mean that there is a phenotypic effect, since CNVs are part of the normal variation of the human genome.⁷¹ However, it has emerged that large, rare CNVs can increase risk of disorder, especially those of a neurodevelopmental nature

such as autism⁷² and mental retardation; thus the advances in technology that have made CNV detection more cost and time effective are very welcome.

Studies of CNVs in ADHD have just started to emerge. The first published study of CNVs in ADHD did not find increased numbers of deletions or duplications in ADHD compared to controls.⁷² However, authors report that the gene set associated with inherited rare CNVs in cases was significantly enriched for genes previously studied in relation to autism, schizophrenia, and Tourette's syndrome.³⁶ Another study of CNVs in ADHD reported rare deletions and duplications in a sample of 99 children and adolescents with severe ADHD.⁷³ One of the duplications encompassed the gene neuropeptide Y (NPY), which has been implicated in behavioral traits and other psychiatric disorders⁷⁴ as well as being involved in energy balance. Although CNV studies in ADHD are still in their infancy, they could point to new risk pathways for ADHD and highlight overlaps across different neurodevelopmental disorders.

Summary and future directions

ADHD is a complex disorder with high heritability. CD may index aetiological as well as clinical heterogeneity. There also appear to be shared inherited links with autism symptoms and CD. Candidate gene association studies have been more successful for ADHD than for other psychiatric disorders, but associated gene variants still explain only a small percentage of the inherited component of ADHD.^{61,75} GWAS on ADHD have only just started to emerge, so it is still too early to completely trust their findings unless

Table 1 Key findings from molecular genetic studies of ADHD

Gene	Type of studies	Evidence	Function
<i>DRD4</i> 7-repeat allele	Association studies and meta-analysis ⁴⁷	Consistent	G protein-coupled receptor that binds dopamine
<i>DRD5</i> 148-bp microsatellite repeat	Association studies and meta-analysis ⁴⁷	Consistent	G protein-coupled receptor that binds dopamine
<i>DAT1</i> 480-bp VNTR	Association studies and meta-analysis ⁴⁷	Mixed evidence	Membrane-spanning protein that removes dopamine from the synaptic cleft
<i>COMT</i> Val ¹⁵⁸ Met	Association studies and meta-analysis ⁴⁷	Not associated with ADHD but associated with CD in ADHD	Enzyme catalyzing the degradation of dopamine, adrenaline and noradrenaline
<i>CDH13</i>	Genome-wide association studies ^{65,67}	Overlap from GWAS studies but needs replication	Cell-cell adhesion protein and regulator of neural cell growth
<i>GFOD1</i>	Genome-wide association studies ^{65,67}	Overlap from GWAS studies but needs replication	Predicted to be involved in electron transport and metabolic processes
<i>TLL</i>	Genome-wide association studies ^{63,65,67}	Overlap from GWAS studies but needs replication	Metalloproteases that cleave collagen, expressed in brain

Abbreviations: GWAS, genome-wide association study; *DRD4*, dopamine D4 receptor gene; *DRD5*, dopamine D5 receptor gene; *DAT1*, dopamine transporter gene; *COMT*, catechol-o-methyltransferase; *CDH13*, cadherin 13; *GFOD1*, glucose-fructose oxidoreductase-domain containing 1; *TLL*, tollid-like genes.

replication in independent samples is achieved. In the future, much larger samples will be required through international collaborative efforts.

Although large samples will be needed, careful, detailed clinical and phenotype assessments are still important. ADHD is heterogeneous and phenotype refinement could potentially lead to more success in identifying genetic risk factors. Also such assessments are important if gene-phenotype links are to be examined. Epidemiological, cognitive neuroscience and imaging studies can also be helpful in examining the risk effects of putative ADHD genes in normal individuals. For example, examining the effects of such genetic variants on brain structure and function as well as other potential “intermediate phenotypes” could help identify risk mechanisms for ADHD as well as a better understanding of brain function in normal individuals.

The next few years are likely to be very exciting for the field of ADHD genetics. The first findings from GWAS are pointing to neuronal cell migration and plasticity but also more basic processes, like cell division and extracellular matrix regulation, which have not been considered before.⁷⁶ New technologies, such as next generation sequencing, are likely to enhance our capacity to examine the contribution of common and rare variants as well as CNVs.⁷⁷ This technology has already been applied to sequence ~1000 human genomes as part of the 1000 genomes project. For the first time an unprecedented amount of genetic variation has become available for testing for association with complex disorders.

To conclude, a number of consistent genetic findings have emerged in relation to ADHD. Advances in technology and statistical analysis methods, improvements in phenotype definition and collaborative efforts to enhance sample sizes will be critical to identify and replicate more susceptibility genes. If and when some of these findings are replicated, the challenge will be to test for causal mechanisms at a biological and clinical level. Such research provides the first step towards understanding the pathogenesis of ADHD and reaching the final goal of improving diagnosis and treatment.

Acknowledgments

Research funding from the Wellcome Trust, Action Medical Research and Baily Thomas Charitable Fund.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005;57(11):1313–1323.
2. Goodman R, Stevenson J. A twin study of hyperactivity – II. The aetiological role of genes, family relationships and perinatal adversity. *J Child Psychol Psychiatry*. 1989;30(5):691–709.
3. Cantwell DP. Genetics of hyperactivity. *J Child Psychol Psychiatry*. 1975;16(3):261–264.
4. Sprich S, Biederman J, Crawford MH, Mundy E, Faraone SV. Adoptive and biological families of children and adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2000;39(11):1432–1437.
5. Levy F, Hay DA, McStephen M, Wood C, Waldman I. Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry*. 1997;36(6):737–744.
6. Thapar A, Holmes J, Poulton K, Harrington R. Genetic basis of attention deficit and hyperactivity. *Br J Psychiatry*. 1999 Feb;174:105–111.
7. Mill J, Petronis A. Pre- and peri-natal environmental risks for attention-deficit hyperactivity disorder (ADHD): the potential role of epigenetic processes in mediating susceptibility. *J Child Psychol Psychiatry*. 2008;49(10):1020–1030.
8. Thapar A, Langley K, Owen MJ, O'Donovan MC. Advances in genetic findings on attention deficit hyperactivity disorder. *Psychol Med*. 2007;37:1681–1692.
9. Thapar A, Langley K, O'Donovan M, Owen M. Refining the attention deficit hyperactivity disorder phenotype for molecular genetic studies. *Mol Psychiatry*. 2006;11(8):714–720.
10. McGough JJ. Adult Manifestations of Attention-Deficit/Hyperactivity Disorder. In: Sadock B, Sadock V, Rouiz P, editors. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*. Vol 2. Philadelphia: Wolters Kluwer; 2009.
11. Stawicki JA, Nigg JT, von Eye A. Family psychiatric history evidence on the nosological relations of DSM-IV ADHD combined and inattentive subtypes: new data and meta-analysis. *J Child Psychol Psychiatry*. 2006;47(9):935–945.
12. McLoughlin G, Ronald A, Kuntsi J, Asherson P, Plomin R. Genetic support for the dual nature of attention deficit hyperactivity disorder: substantial genetic overlap between the inattentive and hyperactive-impulsive components. *J Abnorm Child Psychol*. 2007;35(6):999–1008.
13. Klein RG, Mannuzza S. Long-term outcome of hyperactive children: a review. *J Am Acad Child Adolesc Psychiatry*. 1991;30(3):383–387.
14. Taylor E, Sonuga-Barke E. Disorders of attention and activity. In: Rutter M, Bishop DV, Pine D, et al, editors. *Rutter's Child and Adolescent Psychiatry*. 5th ed. Malden: Wiley-Blackwell; 2008.
15. Larsson H, Lichtenstein P, Larsson JO. Genetic contributions to the development of ADHD subtypes from childhood to adolescence. *J Am Acad Child Adolesc Psychiatry*. 2006;45(8):973–981.
16. Franke B, Vasquez AA, Johansson S, et al. Multicenter analysis of the SLC6A3/DAT1 VNTR haplotype in persistent ADHD suggests differential involvement of the gene in childhood and persistent ADHD. *Neuropsychopharmacology*. 2010;35(3):656–664.
17. Costa e Silva JA. Autism, a brain developmental disorder: some new pathophysiological and genetics findings. *Metabolism*. 2008 Oct;57 Suppl 2:S40–S43.
18. Cuffe SP, Moore CG, McKeown RE. Prevalence and correlates of ADHD symptoms in the national health interview survey. *J Atten Disord*. 2005;9(2):392–401.
19. Reiersen AM, Constantino JN, Grimmer M, Martin NG, Todd RD. Evidence for shared genetic influences on self-reported ADHD and autistic symptoms in young adult Australian twins. *Twin Res Hum Genet*. 2008;11(6):579–585.
20. Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviors in a community twin sample. *J Child Psychol Psychiatry*. 2008;49(5):535–542.

21. Moffitt TE. Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. *Psychol Rev.* 1993;100(4): 674–701.
22. Thapar A, Harrington R, McGuffin P. Examining the comorbidity of ADHD-related behaviors and conduct problems using a twin study design. *Br J Psychiatry.* 2001;179:224–229.
23. Taylor E, Chadwick O, Heptinstall E, Danckaerts M. Hyperactivity and conduct problems as risk factors for adolescent development. *J Am Acad Child Adolesc Psychiatry.* 1996;35(9):1213–1226.
24. Biederman J, Mick E, Faraone SV, et al. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. *Am J Psychiatry.* 2002;159(1):36–42.
25. Rhee SH, Waldman ID, Hay DA, Levy F. Sex differences in genetic and environmental influences on DSM-III-R attention-deficit/hyperactivity disorder. *J Abnorm Psychol.* 1999;108(1):24–41.
26. Rutter M. Gene-environment interdependence. *Dev Sci.* 2007;10(1): 12–18.
27. Linnert KM, Dalsgaard S, Obel C, et al. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry.* 2003;160(6):1028–1040.
28. Thapar A, Rutter M. Do prenatal risk factors cause psychiatric disorder? Be wary of causal claims. *Br J Psychiatry.* 2009;195(2): 100–101.
29. Thapar A, Harold G, Rice F, Langley K, O'Donovan M. The contribution of gene-environment interaction to psychopathology. *Dev Psychopathol.* 2007;19(4):989–1004.
30. Thapar A, Stergiakouli E. Genetic influences on the development of childhood psychiatric disorders. *Psychiatry.* 2008;7(7):277–281.
31. Zhou K, Dempfle A, Arcos-Burgos M, et al. Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2008;147B(8):1392–1398.
32. DiMaio S, Grizenko N, Joobor R. Dopamine genes and attention-deficit hyperactivity disorder: a review. *J Psychiatry Neurosci.* 2003;28(1): 27–38.
33. Gainetdinov RR. Dopamine transporter mutant mice in experimental neuropharmacology. *Naunyn Schmiedeberg's Arch Pharmacol.* 2008; 377(4–6):301–313.
34. Spencer TJ, Biederman J, Madras BK, et al. In vivo neuroreceptor imaging in attention-deficit/hyperactivity disorder: a focus on the dopamine transporter. *Biol Psychiatry.* 2005;57(11):1293–1300.
35. Sharp SI, McQuillin A, Gurling HM. Genetics of attention-deficit hyperactivity disorder (ADHD). *Neuropharmacology.* 2009;57(7–8): 590–600.
36. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. *Hum Genet.* 2009;126(1):51–90.
37. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry.* 2001; 158(7):1052–1057.
38. Li D, Sham PC, Owen MJ, He L. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Hum Mol Genet.* 2006;15(14): 2276–2284.
39. El-Faddagh M, Laucht M, Maras A, Vohringer L, Schmidt MH. Association of dopamine D4 receptor (DRD4) gene with attention-deficit/hyperactivity disorder (ADHD) in a high-risk community sample: a longitudinal study from birth to 11 years of age. *J Neural Transm.* 2004;111(7):883–889.
40. Langley K, Fowler TA, Grady DL, et al. Molecular genetic contribution to the developmental course of attention-deficit hyperactivity disorder. *Eur Child Adolesc Psychiatry.* 2009;18(1):26–32.
41. Shaw P, Gornick M, Lerch J, et al. Polymorphisms of the dopamine D4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry.* 2007;64(8): 921–931.
42. Li J, Wang Y, Zhou R, et al. Association between polymorphisms in serotonin transporter gene and attention deficit hyperactivity disorder in Chinese Han subjects. *Am J Med Genet B Neuropsychiatr Genet.* 2007;144(1):14–19.
43. Lowe N, Kirley A, Hawi Z, et al. Joint analysis of the DRD5 marker concludes association with attention-deficit/hyperactivity disorder confined to the predominantly inattentive and combined subtypes. *Am J Hum Genet.* 2004;74(2):348–356.
44. Maher BS, Marazita ML, Ferrell RE, Vanyukov MM. Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. *Psychiatr Genet.* 2002;12(4):207–215.
45. Purper-Ouakil D, Wohl M, Mouren MC, Verpillat P, Ades J, Gorwood P. Meta-analysis of family-based association studies between the dopamine transporter gene and attention deficit hyperactivity disorder. *Psychiatr Genet.* 2005;15(1):53–59.
46. Yang B, Chan RC, Jing J, Li T, Sham P, Chen RY. A meta-analysis of association studies between the 10-repeat allele of a VNTR polymorphism in the 3'-UTR of dopamine transporter gene and attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2007;144B(4):541–550.
47. Brookes K, Xu X, Chen W, et al. The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. *Mol Psychiatry.* 2006;11(10):934–953.
48. Kahn RS, Khoury J, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *J Pediatr.* 2003;143(1):104–110.
49. Neuman RJ, Lobos E, Reich W, Henderson CA, Sun LW, Todd RD. Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. *Biol Psychiatry.* 2007;61(12):1320–1328.
50. Brookes KJ, Mill J, Guindalini C, et al. A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. *Arch Gen Psychiatry.* 2006;63(1):74–81.
51. Langley K, Turic D, Rice F, et al. Testing for gene x environment interaction effects in attention deficit hyperactivity disorder and associated antisocial behavior. *Am J Med Genet B Neuropsychiatr Genet.* 2008;147B(1):49–53.
52. Laucht M, Skowronek MH, Becker K, et al. Interacting effects of the dopamine transporter gene and psychosocial adversity on attention-deficit/hyperactivity disorder symptoms among 15-year-olds from a high-risk community sample. *Arch Gen Psychiatry.* 2007;64(5):585–590.
53. Cheuk DK, Wong V. Meta-analysis of association between a catechol-O-methyltransferase gene polymorphism and attention deficit hyperactivity disorder. *Behav Genet.* 2006;36(5):651–659.
54. Thapar A, Langley K, Fowler T, et al. Catechol O-methyltransferase gene variant and birth weight predict early-onset antisocial behavior in children with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry.* 2005;62(11):1275–1278.
55. Caspi A, Langley K, Milne B, et al. A replicated molecular genetic basis for subtyping antisocial behavior in children with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry.* 2008;65(2):203–210.
56. Monuteaux MC, Biederman J, Doyle AE, Mick E, Faraone SV. Genetic risk for conduct disorder symptom subtypes in an ADHD sample: specificity to aggressive symptoms. *J Am Acad Child Adolesc Psychiatry.* 2009;48(7):757–764.
57. O'Donovan MC, Craddock N, Norton N, et al. Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nat Genet.* 2008;40(9):1053–1055.
58. Shifman S, Johannesson M, Bronstein M, et al. Genome-wide association identifies a common variant in the reelin gene that increases the risk of schizophrenia only in women. *PLoS Genet.* 2008;4(2):e28.
59. Sullivan PF, Lin D, Tzeng JY, et al. Genomewide association for schizophrenia in the CATIE study: results of stage 1. *Mol Psychiatry.* 2008;13(6):570–584.

60. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007;447(7145):661–678.
61. Weiss LA. Autism genetics: emerging data from genome-wide copy-number and single nucleotide polymorphism scans. *Expert Rev Mol Diagn*. 2009;9(8):795–803.
62. Franke B, Neale BM, Faraone SV. Genome-wide association studies in ADHD. *Hum Genet*. 2009;126(1):13–50.
63. Neale BM, Lasky-Su J, Anney R, et al. Genome-wide association scan of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1337–1344.
64. Zuo L, Kranzler HR, Luo X, Covault J, Gelernter J. CNR1 variation modulates risk for drug and alcohol dependence. *Biol Psychiatry*. 2007;62(6):616–626.
65. Lasky-Su J, Neale BM, Franke B, et al. Genome-wide association scan of quantitative traits for attention deficit hyperactivity disorder identifies novel associations and confirms candidate gene associations. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1345–1354.
66. Uhl GR, Drgon T, Johnson C, et al. Molecular genetics of addiction and related heritable phenotypes: genome-wide association approaches identify „connectivity constellation“ and drug target genes with pleiotropic effects. *Ann NY Acad Sci*. 2008;1141:318–381.
67. Lesch KP, Timmesfeld N, Renner TJ, et al. Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies. *J Neural Transm*. 2008;115(11):1573–1585.
68. Anney RJ, Lasky-Su J, O’Dushlaine C, et al. Conduct disorder and ADHD: evaluation of conduct problems as a categorical and quantitative trait in the international multicentre ADHD genetics study. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1369–1378.
69. Sonuga-Barke EJ, Lasky-Su J, Neale BM, et al. Does parental expressed emotion moderate genetic effects in ADHD? An exploration using a genome wide association scan. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1359–1368.
70. Scherer SW, Lee C, Birney E, et al. Challenges and standards in integrating surveys of structural variation. *Nat Genet*. 2007;39(7 Suppl):S7–S15.
71. Sebat J, Lakshmi B, Malhotra D, et al. Strong association of de novo copy number mutations with autism. *Science*. 2007;316(5823):445–449.
72. Elia J, Gai X, Xie HM, et al. Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. *Mol Psychiatry*. 2010;15:637–646.
73. Lesch KP, Selch S, Renner TJ, et al. Genome-wide copy number variation analysis in attention-deficit/hyperactivity disorder: association with neuropeptide Y gene dosage in an extended pedigree. *Mol Psychiatry*. 2010 Mar 23 [Epub ahead of print].
74. Karl T, Herzog H. Behavioral profiling of NPY in aggression and neuropsychiatric diseases. *Peptides*. 2007;28(2):326–333.
75. Williams HJ, Owen MJ, O’Donovan MC. Schizophrenia genetics: new insights from new approaches. *Br Med Bull*. 2009;91:61–74.
76. Mardis ER. The impact of next-generation sequencing technology on genetics. *Trends Genet*. 2008;24(3):133–141.
77. Siva N. 1000 Genomes project. *Nat Biotechnol*. 2008;26(3):256.

Neuropsychiatric Disease and Treatment

Dovepress

Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the ‘PsycINFO’ database and CAS, and is the official

journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>