Published in final edited form as:
Xin Li Xue Bao. 2008 August ; 40(10): 1088–1098. doi:10.3724/SP.J.1041.2008.01088.

An Overview on the Genetics of ADHD

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Abstract

Attention Deficit Hyperactivity is a childhood-onset disorder that can persist into adult life. Traditional family, twin and adoption studies have shown that ADHD defined both categorically and dimensionally is familial and heritable. Twin studies are now being used to examine ways of defining the ADHD phenotype, to investigate gender differences, the effects on genes on continuity and comorbidity and to consider gene-environment interplay. Molecular genetic findings on ADHD have mainly arisen from functional candidate gene association studies and a number of pooled and meta-analyses have now been conducted. There is consistent evidence of association between ADHD and a dopamine D4 receptor gene VNTR and a dopamine D5 receptor gene microsatellite marker. More recent evidence from different studies and a pooled analysis suggests that conduct problems in those with ADHD is influenced by the *COMT* val158/108 met variant. Linkage studies suggest that there are no genes of moderate effect size and findings from large scale whole genome association studies are currently awaited. Overall the evidence to date, suggests that examining gene-phenotype links and testing whether gene variants have modifying effects on the ADHD phenotype are important. The contribution of gene-environment interplay (G × E) to psychopathology is becoming increasingly recognised, although for ADHD little is known on causal environmental risk factors.

Keywords

ADHD; Twin studies; Molecular genetic findings

Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a childhood-onset disorder that is characterised by developmentally inappropriate, severe, impairing inattention, overactivity and impulsiveness. It is increasingly recognised that ADHD can persist into adolescence and adult life. The reported prevalence of ADHD is between 1.4-5%. Although ADHD is considered as a diagnostic category for clinical purposes, it can also be viewed as a continuously distributed dimension. ADHD is commonly accompanied by other psychiatric and behavioural disorders, notably conduct disorder as well as developmental conditions (e.g. dyslexia, autism), tic disorders, depression and anxiety (Taylor & Sonuga-Barke, 2008). In this review we provide an overview on genetic studies of ADHD. We begin by considering traditional family, twin and adoption study designs. These types of study inform us about the ADHD phenotype that is crucial for informing molecular genetic studies and provideinsights into the origins and development of ADHD. We then move onto review the molecular genetics literature and finally consider future developments.

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Family, twin and adoption studies

These research designs have traditionally been used to examine whether ADHD runs in families and is genetically influenced. More recently twin and family studies have been utilised to examine the genetic validity of different phenotype definitions, gender, developmental continuity and change, comorbidity and gene-environment interplay (Thapar & Rutter, 2008).

Evidence of a genetic contribution to ADHD

Family studies show that the biological relatives of probands with ADHD display higher rates of ADHD than relatives of controls. The relative risk of ADHD in first degree relatives is between 4.0 and 9.0 (Faraone et al, 2000; Chen et al, 2008); thus the familial risk of ADHD is higher than for rheumatoid arthritis but lower than for schizophrenia. Disorders can cluster in families because of shared environment as well as genes. Thus twin and adoption designs are needed to separate these effects.

Twin studies have primarily focused on dimensionally defined ADHD. There have been numerous published studies from across the world showing that ADHD symptoms are highly heritable (Thapar et al, 2006; Faraone et al, 2005); that is most of the individual variation in ADHD scores is attributable to genetic influences. Shared environmental influences that result in greater twin similarity for a given phenotype do not appear to be important. Non-inherited influences must however contribute, as genetic factors do not account for 100% of the phenotypic variation in ADHD. This “left over” non-shared environment variance could be explained by measurement error, random effects including those that are biological (e.g. epigenetic effects) as well as environmental factors that make twins different. The findings of all the published adoption studies are consistent with those of twin studies in demonstrating the importance of genetic influences in ADHD. All of these studies show that adopted children are more similar to their biological relatives than to their adoptive relatives on measures of ADHD.

In summary, there is consistent evidence of a strong genetic contribution to ADHD from family, twin and adoption studies and it is clear that ADHD is also influenced by non-inherited factors.

Defining the ADHD phenotype

1. Which informant and measure?

Most twin studies have obtained maternal ratings of children’s ADHD symptoms using questionnaire measures. Mother’s reports of ADHD scores have been found to be highly heritable with heritability estimates of between 60% - 91% (Thapar et al, 2007). Interestingly many of these studies have found low, near zero or even negative DZ (dizygotic; non identical) twin correlations, particularly where measures with fewer ADHD items have been used. This is thought to arise from rater contrast effects whereby mothers tend to exaggerate twin differences in ADHD symptom levels. This would explain low/negative DZ twin correlations and why DZ/MZ twin variances in ADHD scores differ in some studies. Non additive genetic effects (either genetic dominance or gene-gene interaction) and gene-environment interaction could also account for MZ twin correlations that are much higher than DZ twin correlation coefficients, although it is difficult to distinguish these from rater contrast effects.

Teacher reports of ADHD are also heritable. Twin studies find that most of the phenotypic overlap in terms of mother and teacher reports is due to shared genetic factors. Where

ADHD is defined using both parent and teacher reports, this appears to result in a more reliable, heritable phenotype (Thapar et al, 2006).

Given the increased interest in adolescent and adult ADHD, self reports need to be considered. Twin studies of adolescents and adults show that most of the variation in self reported ADHD scores is attributable to non-shared environmental variance that includes measurement error and heritability estimates are much lower than those found in studies of children where parent and teacher reports have been used (Thapar et al, 2006). Retrospective measures of ADHD in adults have also yielded lower heritability estimates (around 30%) and most of the variance again is accounted for by non shared environmental factors (e.g. Haberstick et al, 2007).

In summary, twin evidence supports the practice of using both mother and teacher reports for defining ADHD in children. In adolescents and adults, the evidence suggests another informant is advisable given some concerns about self reports.

2. ADHD Subtypes

Although DSM-IV allows for subdividing ADHD into combined, hyperactive-impulsive and inattentive subtypes, it is not clear to what extent these are distinct. Family and sibling studies yield mixed findings. Overall results from a meta-analysis and subsequent studies suggest that there is only a small familial effect on subtype distinction and there is evidence for some overlap in terms of shared familial factors (Stawicki et al, 2006). Twin studies have been used to examine whether covariation of hyperactive-impulsive and inattentive symptoms is attributable to shared genetic liability. Most studies have found that there is shared genetic liability. However, others have suggested that there are also distinct genetic and environmental effects on the different symptom groups (Thapar et al, 2006; McLouglin et al, 2007). There is also evidence to suggest that the subtypes are not stable over time (Todd et al, 2008).

Another approach to defining subtypes is to undertake latent class analysis to generate different groups of individuals. A large twin study in Missouri, US derived eight latent classes that were found to be familial and heritable (Todd et al, 2008). A key issue is the extent to which these same latent classes can be derived in other populations. These latent classes have broadly been replicated in other populations and appear to be more consistently independent than DSM-IV subtypes. As a result, some groups have used these classes in molecular genetic studies.

In summary, the genetic evidence in favour of distinguishing ADHD subtypes is mixed.

3. Category or dimension

For clinical diagnostic purposes it is useful to consider ADHD as a categorical entity. However, most twin studies of ADHD have investigated ADHD defined dimensionally. Although fewer twin studies have examined categorical ADHD, those published show that broadly defined categorical ADHD is also heritable. A number of studies have further tested whether there is discontinuity in the genetic aetiology of ADHD scores at the extreme end of the dimension (i.e. higher scores). The genetic contribution to normal variation in ADHD scores seems to be the same as that for high or extreme scores and overlaps with genetic influences on the DSM-IV diagnosis of ADHD (Thapar et al, 2006; Chen et al, 2008; Derks et al, 2008). In summary, it appears that ADHD whether defined dimensionally or categorically is highly heritable and that there is genetic overlap in these constructs.

Gender effects

It is well established that the rate of ADHD is much higher in males than females. It is not clear why and how this male excess arises. One possibility is that there are different risk factors for males and females. Twin and family studies suggest this is not the case. Family studies show that ADHD in females as well as males is familial. Overall most twin studies do not find major differences in the magnitude of genetic influences on ADHD in males and females (Rhee et al, 1999) and also have been unable to demonstrate that there are different sets of male and female genetic influences.

Developmental change and continuity

Longitudinal studies of ADHD show that there is considerable diagnostic persistence and symptom continuity over time. There has been one family study that suggests that persistent ADHD may define a more strongly familial subtype (Faraone et al, 2000). Longitudinal twin studies show that most symptom continuity over time (in early, mid-childhood and adolescence) is attributable to genetic influences (e.g. Kuntsi et al, 2005; Larsson et al, 2006). Some have also found that there are additional separate genetic influences that contribute to ADHD symptoms in older children and adolescents. In summary, genetic factors not only contribute to the origins of ADHD but also contribute to continuity and persistence.

Comorbidity

ADHD and conduct problems commonly co-occur, in clinical populations (conduct disorder or oppositional defiant disorder) and at a symptom level in the general population and twin studies show that this arises because of shared genetic liability for the two phenotypes (Faraone et al, 2005; Thapar et al, 2006). A somewhat different question relates to whether or not children with categorically defined ADHD who also have conduct problems are different to those without conduct problems in terms of familial and genetic loading especially as they are known to have worse outcomes. Family studies suggest that ADHD and conduct disorder is a more strongly familial category than ADHD alone (Faraone et al, 2000). Findings from a subsequent twin study have also shown that comorbid conduct problems indexes higher genetic loading in ADHD (Thapar et al, 2001). Recent work suggests that ADHD with conduct disorder problems vs. ADHD alone are not qualitatively distinct entities (Rhee et al, 2008). As a result of these findings, a number of molecular genetic studies have utilised conduct disorder/ODD as an index of ADHD heterogeneity. ADHD also co-occurs with reading disability (the overlap appears to be stronger with inattention symptoms) and autistic traits. Twin studies suggest that these phenotypic overlaps are also attributable to shared genetic influences (Wilcutt et al, 2007; Ronald et al, 2007; Reiersen et al, 2007). Overall these findings suggest that the same genetic risk variants may contribute liability to ADHD and these different phenotypes.

Gene-environment interplay

Genes and environmental influences work together in complex ways (Plomin et al, 2008; Rutter 2007). There is increasing evidence that gene-environment correlation and gene-environment interaction are important in the aetiology of psychopathology.

1. Gene-environment correlation

Here, genetic and environment risk factors co-occur in a non-random fashion because heritable characteristics of the individual or parents create risk for exposure to certain environmental risk factors. This means that the risk effects of genes and environment are not necessarily distinct and also that genes may indirectly increase risk for ADHD by

influencing exposure to risk or protective environments. This is certainly important for other psychopathology such as depression and emerging evidence suggests the likely importance of gene-environment correlation for ADHD (Lifford, Harold & Thapar, in preparation).

2. Gene-environment interaction

Gene-environment interaction occurs where the risk or protective effects of genetic factors depends upon the presence of a specific environmental factor (Thapar et al, 2007b; Rutter, 2007). Gene-environment interaction (GXE) can be examined using twin or adoption study designs or through molecular genetic study designs. These methods examine gene-environment interaction in different ways. So far, there have been no published twin studies examining gene-environment interaction for ADHD. However more knowledge is needed on likely causal environmental risk factors for ADHD. Risk factors that are associated are not necessarily causal (Rutter, 2007). Molecular genetic studies testing for GXE are described later.

Molecular genetics of ADHD—ADHD is a complex disorder and as such is most likely influenced by a large number of genes as well as environmental factors. Thus far, the quest of identifying susceptibility genes has been based on three main approaches (Thapar & Rutter, 2008). The first strategy involves genotyping many genetic markers across the genome in families where multiple members are affected (usually sibling pairs). This method highlights chromosomal regions that are shared more often than expected by affected relatives. Regions identified by these whole genome linkage studies are usually large and fine mapping strategies are required to identify genes (Plomin et al, 2008). The second approach requires an *a prior* hypothesis about the likely involvement of a candidate gene in the disorder. There are two types of these candidate gene studies: case-control studies, where the allele frequencies are compared between ADHD patients and healthy controls and family-based studies, where parents serve as controls. Functional candidate genes are selected because they are considered to be involved in disease pathophysiology. Positional candidates are selected because of their chromosomal positions (for example, informed by linkage studies). Finally and most recently a new generation of genetic studies has become feasible. Whole genome association (WGA) studies examine thousands or even millions of markers across the genome and they promise to yield novel, hypothesis-free results. Initial findings for other disorders appear promising (e.g., Wellcome Trust Case Consortium, 2007). Currently, three WGA studies for ADHD are under way and should be completed by the end of 2008. To date, most molecular genetic findings for ADHD have arisen from functional candidate gene association studies.

Whole genome linkage studies

Whole genome linkage scans have been based either on the affected sibling pair (ASP) or the extended pedigree approach. At the time of writing, results of seven linkage studies of ADHD have been published (Table 1); five using ASPs and two using multiplex families. As table 1 suggests, there is some overlap in significant linkage peaks. Evidence for at least nominally significant linkage has been found more than once for chromosomal regions 5p13, 16p13 and 17p11.

A study of 126 ASPs from USA provided weak evidence for linkage at 16p13 (Fisher et al. 2002), which has also been implicated in autism. Stronger evidence for 16p13 [LOD (logarithm of the odds) score 4.2] came from an expanded sample of 203 ASPs (Smalley et al, 2002). The same region also came up in a study of 308 American ASPs with an MLS (Maximum Multipoint LOD) of 3.73 (Ogdie et al, 2004).

The chromosomal region at 5p13 also came up in the latter study (Ogdie et al, 2004). Modest evidence for linkage for the same region (MLS=1.43) appeared in a study of 164 Dutch ASPs (Bakker et al, 2003). Pooled analysis of the American and Dutch samples (Ogdie et al, 2006) yielded significant evidence of linkage (MLS=3.67) for 5p13, although the signal appeared to be coming mainly from the American families suggesting sample heterogeneity had an impact on the results. Finally, Hebebrand et al. (2006) studied 155 ASPs from Germany and found weak evidence of linkage (MLS=2.59) on chromosome 5p at 17cM. Another interesting region is 17p11, as there is evidence of linkage in both the study of 308 ASPs from USA (Ogdie et al, 2004) with an MLS of 3.63, as well as from the study of German ASPs (Hebebrand et al, 2006). A study with a different design using 16 multigenerational and extended pedigrees from Colombia also reported weak evidence of linkage at 17p11 (Arcos-Burgos et al, 2004).

In summary, whole genome linkage studies have yielded some interesting results for chromosomal regions that need to be further investigated. It seems difficult to achieve replication of genome-wide significant results, suggesting that there are no susceptibility genes of large effect for ADHD. For this reason, an association approach is likely to be more suitable, since it can identify genes of smaller effect.

Functional candidate gene association studies

Due to the large number of such studies, this review will only focus on genes where significant findings have stood up to meta-analyses or pooled analyses or where there have been replications. Many of these functional candidate genes have been selected because they code for proteins or enzymes involved in the dopamine pathway. Interest in the dopaminergic system in ADHD has come from pharmacological, animal and imaging studies. First, stimulant medication, such as methylphenidate, reduces ADHD symptoms and inhibits the reuptake of dopamine thus increasing its extracellular concentration (DiMaio et al, 2003). In addition, imaging studies of patients with ADHD provide evidence of changes in brain regions where dopaminergic systems are more active (Spencer et al, 2005). Finally, animal studies, such as work on the DAT knockout mouse which manifests ADHD-like behaviour, have also implicated dopaminergic systems (Gainetdinov, 2007). All this evidence has led to the investigation of *DRD4, DRD5, SLC6A4* and *COMT* which will be discussed. Other genes such as those encoding dopamine beta-hydroxylase, monoamine oxidase A, the dopamine D2 and dopamine D3 receptors have also been investigated but the results are not yet conclusive. Nearly all the published molecular genetic studies of ADHD have been based on clinical cases where ADHD has been defined according to DSM-IV diagnostic criteria. A few studies have examined ADHD defined dimensionally but the association findings here have generally been weaker (Mill et al, 2005).

1. Dopamine D4 receptor gene (*DRD4*)

The *DRD4* gene is on chromosome 11p15.5. The D4 receptor binds both dopamine and noradrenaline. Most studies have focused on a variable number tandem repeat (VNTR) polymorphism in exon III of the gene. The number of repeats ranges from 2-11 with different populations having different alleles. This polymorphism is supposed to be functional, since the 7-repeat allele reduces the ability of the receptor to bind dopamine according to *in vitro* studies. The first meta-analysis of the *DRD4* gene in ADHD (Faraone et al, 2001) found significant association between the 7-repeat allele and ADHD in both case-control studies [OR (odds ratio) =1.9, 95% CI (confidence interval) 1.4-2.2] and family-based studies (OR=1.4, 95% CI 1.1-1.6). More recently, the same group conducted a pooled analysis and found that the association with ADHD was still significant in both case-control studies (OR=1.45, 95% CI 1.27-1.65) and family-based studies (OR=1.16, 95% CI 1.03-1.31) (Faraone et al, 2005). Li et al. (2006) included 33 association studies in their

meta-analysis and also obtained strong evidence that the 7-repeat allele ($P=2 \times 10^{-12}$, OR=1.34, 95% CI 1.23-1.45) is associated with ADHD. They also suggested that the 5-repeat allele (P=0.005, OR=1.68, 95% CI 1.17-2.41) confers increased risk for ADHD and concluded that the 4-repeat allele has a protective role (P=0.004, OR=0.90, 95% CI 0.84-0.97) (Li et al, 2006) but that evidence is not clear-cut. Since this last meta-analysis, further association studies of *DRD4* have been published. A longitudinal study from Germany replicated the association between ADHD and the 7-repeat allele (El-Faddagh et al, 2004). However, Brookes et al. (2006a) in a study of 776 ADHD cases from the International Multi-centre ADHD Gene (IMAGE) project failed to replicate this association.

The *DRD4* 7-repeat allele has also been reported to influence cognitive performance but findings here are mixed with some studies showing that those with the 7-repeat allele perform worse on measures of accuracy and cognitive ability and other groups finding better performance in those with the risk allele, so no conclusions can yet be drawn (Thapar et al, 2007a). There have also been longitudinal studies suggesting that those with ADHD who possess the *DRD4* 7 repeat allele show a poorer outcome (Mill et al, 2005; El Faddagh et al, 2004; Langley et al, 2008). However again, findings have not been entirely consistent (Shaw et al, 2007).

2. Dopamine D5 receptor gene (*DRD5*)

Another dopamine receptor gene, *DRD5*, on chromosome 4p15.1-15.3 also appears to be important. The associated polymorphism is a microsatellite (a dinucleotide repeat with variable number of copies) mapping 18.5 kb away from the 5′ end of the gene (Daly et al, 1999). The first meta-analysis of *DRD5* included 5 studies and showed a significant association with the 148-bp allele (Maher et al, 2002). Significant association (OR=1.24, 95% CI 1.1-1.4) with the same allele was also reported by a joint analysis of 14 independent studies resulting in approximately 2000 ADHD cases (Lowe et al, 2004). Association was considered to be stronger in those with ADHD inattentive type. Finally, Li et al. (2006) included 9 association studies of *DRD5* and also concluded that the 148-bp allele of *DRD5* confers risk for ADHD. These authors also suggested that the 136-bp allele of *DRD5* has a protective role. However, a study of 329 male twins examining a trait measure of ADHD, found association with the same variant but in the opposite direction, that is, the 148-bp allele had a protective role (Mill et al, 2005). Association with ADHD has also been shown for other polymorphisms in *DRD5* including two microsatellites at the 5′ end of the gene and a SNP in the 3′ UTR (Untranslated Region) of *DRD5* but these have been less widely studied.

3. Dopamine transporter gene (*SLC6A3* or *DAT1*)

The dopamine transporter gene on chromosome 5p13.3 was initially considered the most likely candidate gene for ADHD. The major reason being that it is responsible for the reuptake of dopamine in the presynaptic cleft and is the target of stimulant medication (DiMaio et al, 2003). Another reason for considering *SLC6A3* an important candidate gene for ADHD is because the DAT knockout mouse model exhibits hyperactivity and deficits in inhibitory behaviour. Treating these mice with stimulants reduces symptoms (Gainetdinov et al., 2007).

Despite these findings, association studies have not been able to produce clear evidence about the involvement of *SLC6A3* in ADHD. The best studied polymorphism is a VNTR in the 3′ UTR of the gene. The first meta-analysis of nine *SLC6A3* studies in ADHD reported an OR of 1.27 with a trend for association with the 480-bp allele (p=0.063) (Maher et al, 2002). Similar results were produced by Curran et al. (2005) based on 11 studies (two more than the previous meta-analysis). Nevertheless, both studies found evidence of heterogeneity

across samples. In an updated meta-analysis by Faraone et al. (2005) the association of the 480-bp allele was significant, although the OR=1.13 (95% CI 1.03-1.24) was small. Another meta-analysis of 12 family-based studies the same year failed to find any association of the *SLC6A3* with ADHD (Purper-Ouakil et al, 2005). No association of the 480-bp allele of *SLC6A3* with ADHD was also found in the meta-analysis by Li et al. (2006). The most recent meta-analysis showed a small but significant association (p=0.004, OR=1.17, 95% CI 1.05-1.30) for TDT studies but not for haplotype-based studies or case-control studies (Yang et al, 2007). However, the number of haplotype-based and case- control studies was small (Yang et al, 2007). Apart from the 3′ UTR VNTR, association has been reported for a SNP (rs40184) in the IMAGE sample (Brookes et al, 2006a). Haplotypes that include the 3′ UTR VNTR and other microsatellite repeats have also been found to be associated with increased risk for ADHD (Asherson et al, 2007; Brookes et al, 2006b).

The evidence overall from an abundance of meta-analytic studies is inconsistent. One possibility is that the effect size of this variant is very small. Another possibility is that the polymorphism in question is not directly responsible for increasing risk for ADHD but is in linkage disequilibrium with another functional polymorphism. After all, it is in the 3′ UTR of the gene, which as the name suggests, is transcribed to mRNA but not translated into protein, thus its function is questionable. It is worth noting that most of the meta-analyses have found evidence of sample heterogeneity.

Another possibility for non-replication is gene-environment interaction (Thapar et al, 2007b). One study of ADHD found evidence of interaction between the haplotype containing the 3′ UTR VNTR and exposure to maternal alcohol consumption during pregnancy (Brookes et al, 2006b) but this requires replication. Two studies suggested that those with the 480bp (10 repeat) allele who were exposed to maternal smoking in pregnancy showed higher levels of ADHD symptoms. However another study found evidence of GXE for the 9 repeat allele in relation to exposure to maternal smoking in pregnancy (Neuman et al, 2007) and a different group failed to replicate these findings (Langley et al, 2007).

4. Catechol-O-Methyltransferase (*COMT*)

The gene encoding COMT, an enzyme catalyzing the degradation of dopamine, adrenaline and noradrenaline, is on chromosome 22q11.2. Interest in *COMT* comes from its involvement in dopaminergic pathways. The most studied polymorphism in *COMT* is a SNP resulting in a valine to methionine substution. This polymorphism is functional with the val/val genotype increasing enzyme activity.

Virtually no individual studies and two pooled analyses (Cheuk and Wong 2006; Faraone et al. 2005) have found evidence of associated between this variant and ADHD. Interestingly the, *COMT* Val allele yielded an almost significant result in the male group of the Cheuk and Wong (2006) meta-analysis. Thus, it could potentially be involved in male susceptibility to ADHD (Cheuk and Wong 2006).

In contrast there is evidence that the *COMT* val/val genotype is associated with conduct disorder symptoms in patients with ADHD (Thapar et al. 2005). Since this first report, the same genotype was subsequently found to be associated with antisocial behaviour in those with ADHD (but not in those without ADHD) in two independent populations from a UK and a New Zealand birth cohort (Caspi et al. 2008). A pooled analysis of four studies also showed significant association with the val/val genotype (Caspi et al, 2008). These results suggest that some gene variants operate by modifying the ADHD phenotype rather than by increasing risk.

5. Synaptosomal-associated protein of 25kD (*SNAP25*)

SNAP25 is a neuron specific protein involved in the regulation of neurotransmitter release. It emerged as a candidate gene for ADHD when it was discovered that the coloboma mouse mutant, which lacks a chromosomal region containing *SNAP25* as well as other genes, exhibits hyperactivity that could be reduced by the use of stimulant medication D-amphetamine.

Currently there is only one meta-analysis including this gene which reported a significant association with the T1065G SNP at the 3′ end of the gene (Faraone et al, 2005). Nominally significant association with *SNAP25* was also reported using the IMAGE sample, although the group tested different markers (Brookes et al. 2006a). A study of 12 SNPs in *SNAP25* using two independent samples also yielded evidence of association but in only one of the samples (Feng et al, 2005). Finally, Kim et al. (2007) reported a modestly significant association with two SNPs that have not been studied before in a TDT analysis. Interestingly, in this study, a stronger association with *SNAP25* was found in patients with ADHD and comorbid depression highlighting the importance of taking into account psychiatric comorbidity in association studies (Kim et al, 2007).

To summarize, the most robust evidence is for an association between the *DRD4* VNTR and *DRD5* microsatellite marker in ADHD. (Table 2 summarizes all the meta-analyses for the genes discussed). It is still unclear whether the *DRD4* VNTR is causal. The *DRD5* 148-bp microsatellite is 18.5kb away from the gene but that does not mean it does not influence DRD5 in a yet unknown fashion. As for *SLC6A3*, most studies have been negative or inconclusive, although it initially appeared as the strongest candidate gene. One explanation could be that the *SLC6A3* 480-bp VNTR is not responsible for the association but is tagging the functional polymorphism which is yet to be found. The evidence that *COMT* val/val genotype has a modifying effect on antisocial behaviour in ADHD is also fairly strong. Further studies on *SNAP25* are needed before conclusions can be drawn.

Future—This review has highlighted that a number of consistent genetic findings have emerged in relation to ADHD. So what are the likely future directions? Traditional family, twin and adoption designs are no longer needed to test whether ADHD is genetically influenced. That is now known. However, these methods are still useful for examining important clinical and developmental questions that remain unanswered. These designs also provide evidence that can guide molecular genetic studies. For example, research on phenotype definition, phenotypic overlap and intermediate phenotypes are likely to be important. Genetically sensitive designs, such as twin studies will also be useful for investigating causal environmental risk factors for ADHD. This is important now we are entering the era of testing for gene-environment interaction. Such analyses must be guided by prior knowledge as to whether a given environmental risk factor is truly causal. Another example of gene-environment interaction is the study of genetic variants influencing drug response known as pharmacogenetics. Identifying factors that influence treatment response may be helpful although thus far, there have been no consistent findings and risk effects may be too small to have immediate impact on clinical practice.

Laboratory and statistical genetic methods will undoubtedly develop even further in the next few years. Published results from WGA studies of ADHD are currently awaited. It is already clear, however, from WGAS of other phenotypes that very large sample sizes are needed to detect genetic risk variants of small effect size and that international collaboration is necessary to achieve this aim. There is increasing interest in the potential role of sub-microscopic chromosomal changes (copy number variants) to complex diseases and the contribution of rare variants to neurodevelopmental disorders (Abrahams & Geschwind, 2008). Thus it is also important to consider these possibilities for ADHD.

Examining gene-phenotype links will remain important. In recent years, there has also been increasing interest in cognitive and neuroimaging phenotypes. Although ADHD is defined according to reported clinical symptoms, it is also characterised by a range of cognitive deficits, as evaluated by different cognitive tasks and differences in brain structure and function compared to typically developing children. Cognitive and imaging measures are not used to make a diagnosis of ADHD but are of interest to researchers who are attempting to examine the pathways from risk factor to disorder and identify intermediate phenotypes. Due to phenotyping costs, it is difficult to undertake genomic and cognitive imaging work on a very large scale. Nevertheless, such studies, although not used for gene discovery, will still be useful for examining the phenotypic effects of identified gene variants. Although there are many criticisms of current clinical diagnostic criteria, there is still the need to understand the aetiology of a phenotype that is relevant to clinicians and patients. Finally, one of the key goals of genetic studies of ADHD is to understand its aetiology and mechanisms. The challenge undoubtedly will not only be in identifying risk factors but more importantly testing causal mechanisms. Proving causality of genetic risk variants at a biological and phenotypic level undoubtedly represents a challenge but an important and interesting one that will need to be tackled by researchers in innovative ways.

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Table 1

Summary of ADHD whole genome linkage studies published so far

(Regions that show overlap in different studies are in bold)

Study	Size and design	Sample origin	Chromosomal regions	Evidence of linkage
Fisher et al. 2002	126 ASPs	USA	No evidence of linkage	-
Smalley et al. 2002	203 ASPs	USA	**16p13**	4.2
Ogdie et al. 2003	270 ASPs	USA	**16p13**	4
Ogdie et al. 2004	308 ASPs	USA	**5p13**	2.55
			6q12	3.3
			16p13	3.73
			17p11	3.63
Ogdie et al. 2006	424 ASPs	USA and Dutch	**5p13**	3.67
Bakker et al. 2003	164 ASPs	Dutch	15q15	3.54
			7p13	3.04
			5p13	1.43
Arcos-Burgos et al. 2004	16 extended pedigrees	Colombian	**17p11**	MLS=1.42
Hebebrand et al. 2006	155 ASPs	German	**5p**(at 17cM)	2.59
			17p	3.37(for inattention only) Nominally significant
Faraone *et al.* 2007	601 ASPs	USA	No significant or suggestive linkage	-
Romanos et al. 2008	8 extended pedigrees	German	5q13	4.16
			14q12	4.5
			2q35	3.4
Asherson et al. 2008	142 ASPs	IMAGE sample	16q23	3.1
			9q22	2.13

ADHD: Attention Deficit Hyperactivity Disorder; ASPs: Affected Sibling Pairs; MLS: Maximum Multipoint LOD; IMAGE: International Multi-centre ADHD Gene

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Table 2

Meta-analyses and pooled studies for candidate gene association studies of ADHD

Gene	Reference	Type of studies included	OR	95% CI	p value
DRD4 7-repeat allele	Faraone et al. 2001	Case-control	1.9	1.4-2.2	<0.001
		Family-based	1.4	1.1-1.6	0.02
	Faraone et al. 2005	Case-control	1.45	1.27-1.65	-
		Family-based	1.16	1.03-1.31	-
	Li et al. 2006	Case-control and family-based	1.34	1.23-1.45	2×10^{-12}
DRD4 5-repeat allele	Li et al. 2006	Case-control and family-based	1.68	1.17-2.41	0.005
DRD5 148-bp microsatellite repeat	Maher et al. 2005	Family-based	1.57	1.25-1.96	0.00008
	Lowe et al. 2004a	Family-based	1.24	1.1-1.4	0.00005
	Li et al. 2006	Case-control and family-based	1.34	1.21-1.50	8×10^{-8}
SLC6A3 480-bp VNTR	Maher et al. 2002	Family-based	1.27	0.99-1.62	0.063
	Curran et al. 2005	Family-based	1.15	-	0.06
	Faraone et al. 2005	Family-based	1.13	1.03-1.24	-
	Purper-Ouakil et al. 2005	-	1.19	0.99-1.41	0.21
	Li et al. 2006	Case-control and family-based	1.04	0.98-1.11	0.20
	Yang et al. 2007	Family-based	1.7	1.05-1.30	0.004
		Case-control	0.95	0.8-1.12	0.54
		Haplotype-based	1.5	0.97-2.33	0.07
COMT $Val^{158}Met$	Faraone et al. 2005	Case-control	1.0	-	-
		Family-based			

Gene	Reference	Type of studies included	OR	95% CI	p value
	Cheuk and Wong, 2006	Case-control and family-based	0.99	0.88-1.12	0.87
SNAP25 T1065G	Faraone et al. 2005	Case-control and family-based	1.19	1.03-1.38	-

ADHD: Attention Deficit Hyperactivity Disorder; OR: Odds Ratio; CI: Confidence Interval

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