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INVITED REVIEW

Advances in genetic findings on attention deficit hyperactivity disorder

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a common, childhood-onset neurodevelopmental disorder with adverse consequences during adult life. Family, twin and adoption studies show that genetic factors contribute to the aetiology of ADHD and that environmental factors also play a role. Family and twin studies have shown the importance of genetic influences on continuity in ADHD over time and in accounting for the co-occurrence of ADHD and conduct disorder problems. In meta-analyses of molecular genetic studies, the 48-bp variable number tandem repeat (VNTR) variant in the dopamine D4 gene and the CA(n) microsatellite marker in the D5 receptor gene have been found to be repeatedly associated with ADHD. Results from meta-analyses of the 480-bp VNTR in the dopamine transporter gene are mixed. Several genetic studies have also identified genetic variants that are related to specific clinical and developmental features of ADHD. In the next few years, a new generation of much larger-scale genetic studies should lead to the identification of further ADHD susceptibility genes. Such studies will also need to be integrated with other areas of neuroscience, clinical and epidemiological research to investigate how specific gene variants exert risk effects, interact with environmental factors and enable identification of the underlying causal mechanisms that lead to ADHD.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset, neurodevelopmental condition characterized by developmentally inappropriate inattention, motor over-activity and impulsiveness (Taylor *et al*. 1991). For an individual to meet DSM-IV criteria for ADHD or ICD-10 criteria for hyperkinetic disorder, these symptoms need to cause impairment and be exhibited in different settings, for example at home and at school or work. The DSM-IV system also allows for subtyping of ADHD into predominantly inattentive type, hyperactive-impulsive type, and a combined type that is most similar to the ICD-10 concept of hyperkinetic disorder (Barkley, 1998). ADHD affects between 2% and 5% of children (Faraone *et al*. 2003) and it is now recognized that ADHD can persist into adolescence and adult life, although it is not yet clear how diagnostic criteria are best adjusted for the developmental phase (Faraone *et al*. 2004). In a recent study in the USA, the estimated prevalence rate of current adult ADHD was 4·4% (Kessler *et al*. 2006).

The aetiology of ADHD, as for other psychiatric disorders, is complex (Thapar *et al*. 2006). Genetic, prenatal and later environmental influences all appear to increase susceptibility to ADHD and are also likely to modify its course and outcome.

Evidence of a genetic contribution to ADHD

It is now well established that ADHD runs in families and is strongly genetically influenced. This evidence comes from family, twin and adoption studies (Thapar *et al*. 1999; Faraone *et al*. 2005).

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Studies comparing the families of clinic-referred children with ADHD to relatives of referred children with other disorders and normal controls have found increased rates of ADHD in all closely related family members of affected probands including siblings (Faraone *et al.* 1991; Biederman *et al.* 1992) and parents (Biederman *et al.* 1991, 1992). Family studies have also found that half-siblings of ADHD children reared together with an ADHD proband have a significantly lower risk of developing the disorder than full siblings of the proband (Goodman & Stevenson, 1989), indicating that familial clustering is unlikely to result exclusively from the family environment. Overall, the relative risk of ADHD in first-degree relatives of probands with the disorder is between 4·0 and 5·4 (Faraone *et al.* 2000).

Adoption study findings are consistent with genetic factors contributing to the familiality of ADHD (Cantwell, 1975; Cunningham *et al.* 1975; Alberts-Corush *et al.* 1986; Sprich *et al.* 2000). All published studies show that adopted children with ADHD are more similar to their biological parents on ADHD measures than to their adoptive parents. Although clearly indicating a genetic contribution to ADHD, adoption studies have been criticized for limitations such as small sample sizes and the fact that interviewers are generally not blind to psychiatric or adoptive status (McMahon, 1980).

Twin studies have also consistently found a large, significant contribution of genetic factors to variation in ADHD (Thapar *et al.* 1999; Faraone *et al.* 2005). The twin studies have differed from those based just on families, biological and adoptive, in that they mostly have been population-based, questionnaire studies and are therefore more representative of the general population. The results indicate high heritability of ADHD, with between 60% and 91% of the variance in ADHD scores in the general population being explained by genetic factors (Thapar *et al.* 1999). ADHD is similarly heritable when conceptualized categorically (Goodman & Stevenson, 1989; Sherman *et al.* 1997; Thapar *et al.* 2000; Price *et al.* 2001).

Genetic contribution to ADHD subtypes, persistence and co-morbidity

Family and twin study designs have also been used to examine questions other than whether genetic factors influence ADHD. First, there is the issue of whether different ADHD subtypes show a distinct genetic architecture. Findings on the extent to which DSM-IV inattentive and hyperactive-impulsive subtypes are influenced by a different or shared set of genetic factors are, however, mixed (Sherman *et al.* 1997; Hudziak *et al.* 1998; Faraone *et al.* 2000; Smalley *et al.* 2000; Todd *et al.* 2001; Rasmussen *et al.* 2004; Larsson *et al.* 2006). Family studies of clinical samples have found that the subtypes tend to breed true, whereas population-based twin studies have shown a shared genetic contribution to different subtype dimensions (Thapar *et al.* 2006). As an alternative to the DSM-IV method of subtyping, a number of studies have also used latent class analysis to identify statistically derived latent subtypes of the disorder. These studies find significant genetic contributions to latent (or underlying) ADHD constructs (Neuman *et al.* 2001; Todd *et al.* 2002) that have been used by some of these research groups in subsequent molecular genetic studies.

Second, the developmental course of ADHD has been examined. Cross-sectional family studies suggest that the relative risk of ADHD may be higher in relatives of first-degree relatives of those with persistent ADHD (λ_r = 17·2–19·7; λ_r is a measure of risk for ADHD in relatives) than those with childhood ADHD (λ_r = 4–5·4) (Faraone *et al.* 2000). Longitudinal twin study findings have additionally shown that it is genetic influences that are the main contributor to stability of ADHD symptoms over time (Nadder *et al.* 2002; Larsson *et al.* 2004; Rietveld *et al.* 2004; Kuntsi *et al.* 2005; Price *et al.* 2005).

Finally, ADHD commonly co-occurs with other disorders, especially conduct disorder. Twin studies have been consistent in showing that the co-occurrence of ADHD and conduct disorder symptoms is accounted for by shared genetic factors (Silberg *et al.* 1996; Thapar *et al.* 2001). There is also evidence from family (Faraone *et al.* 2000; Smalley *et al.* 2000) and twin studies (Thapar *et al.* 2001) that ADHD accompanied by conduct disorder problems is more strongly familial (λ_r = 4·8–9·5) than ADHD alone (Faraone *et al.* 2000) and indexes higher genetic loading.

In summary, there is evidence from different sources showing that ADHD is genetically

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Table 1. *Significant and suggestive findings from whole-genome linkage studies into ADHD*

Chromosome	German ASP sample ($n=155$)[a]	Colombian sample ($n=16$ families)[b]	Utrecht ASP sample ($n=164$)[c]	Los Angeles ASP simple ($n=308$)[d]	Combined Utrecht and Los Angeles ASP samples ($n=424$)[e]
5p13				2·55	3·67
5p17	2·57				
6q12				3·30	
7p13			3·04		
15q15			3·54		
16p13				3·73	
17p11		1·42		3·63	

ADHD, Attention deficit hyperactivity disorder; ASP, affected sib pair.
[a] Heiser *et al.* 2006.
[b] Arcos-Burcos *et al.* 2004.
[c] Bakker *et al.* 2003
[d] Ogdie *et al.* 2003, 2004.
[e] Ogdie *et al.* 2006.

influenced. Family and twin studies also suggest that genetic factors play an important role in ADHD persistence and contribute to the co-occurrence of conduct disorder.

Molecular genetic studies

The process of identifying susceptibility genes for complex disorders has, until recently, either involved searching the whole genome using linkage strategies or more targeted candidate gene association approaches (Faraone *et al.* 2005). Most recently, whole genome association (WGA) studies based on several hundreds of thousands of genetic markers have become feasible. At the time of writing, WGA studies of ADHD are under way, but none have yet been published. Thus, to date, genetic findings implicating specific susceptibility genes for ADHD have all been the fruit of functional candidate gene studies.

Linkage study findings for ADHD

So far, findings from four whole-genome linkage studies have been published (see Table 1). Three are affected sib pair (ASP) linkage studies from the USA (Fisher *et al.* 2002; Smalley *et al.* 2002; Ogdie *et al.* 2003, 2004, 2006), the Netherlands (Bakker *et al.* 2003) and Germany (Heiser *et al.* 2006) and the other study is based on multiplex families from Colombia (Arcos-Burgos *et al.* 2004) (see Table 1). In the Dutch study (Bakker *et al.* 2003), which included 164 ASPs, there was suggestive evidence of linkage (the finding did not reach statistical significance but the signal was large enough that we would expect it to be picked up by chance only once per genome scan) on chromosomes 7p and 15q [maximum Multipoint LOD (logarithm of the odds) Scores (MLSs) = 3·04 and 3·54]. In the USA (UCLA) study of 270 ASPs (Ogdie *et al.* 2004), significant linkage was found on chromosome 16p13 (MLS = 3·73) and suggestive linkage on 17p11 (MLS = 2·98). One region, 5p13, showed modest evidence of linkage (LOD score >1) in both studies, with an MLS of 1·43 in the Dutch sample and 1·77 in the US sample. Linkage analysis of the joint UCLA and Dutch (Ogdie *et al.* 2006) sample yielded significant evidence for linkage at 5p13 (MLS = 3·67, $p=0·01$). The authors, however, found that this signal came mainly from the UCLA families and also found evidence for distinct genetic backgrounds for each sample, possibly indicating ethnic or sample collection differences. The robustness of these findings therefore requires further investigation.

Fine mapping studies are in progress, as are results from other linkage studies across the world. The most recently reported fine mapping results of positional candidate regions using 308 ASPs from UCLA supported significant evidence of linkage (Ogdie *et al.* 2004) in the previously identified candidate linkage regions on 17p11 and 16p13. These analyses also highlighted suggestive evidence of linkage in a new region on 6q12, as well as on chromosome 5p13. The study from Colombia differs in that it was based on 16 multigenerational and extended pedigrees (Arcos-Burgos *et al.* 2004). Although

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linkage analysis on the combined set of families showed peaks (MLS >1) on chromosomes 5q33.3, 11q22 and 17p11, these did not achieve conventional levels of statistical significance ($\alpha = 0{\cdot}10$). Fine mapping linkage analysis of all families together yielded significant linkage at chromosomes 4q13.2, 5q33.3, 11q22 and 17p11. The only region of overlap with previous studies was 17p11. In summary, to date there have been few published linkage studies of ADHD and results are at an early stage.

Functional candidate gene association studies

Functional candidate gene studies based on guesses about pathophysiology have not been very successful in complex diseases as a whole, possibly because the hypotheses of causation are not correct. They have, however, been remarkably successful for ADHD, where selection of functional candidate genes has been informed by findings from a variety of sources, including those from animal, pharmacological and imaging studies. These studies have particularly pointed to the likely involvement of dopaminergic pathways in ADHD, although clearly other neurotransmitter systems are also likely to be involved, as are biological mechanisms not based simply on neurotransmitters. First, for ADHD there is well-established evidence of an immediate and in most cases robust response to stimulant medication. These pharmacological agents, notably methylphenidate, appear to exert therapeutic effects in ADHD by increasing the functional availability of extracellular dopamine (Volkow & Swanson, 2003) through inhibition of the dopamine transporter (DAT1, encoded by the gene *SLC6A3*), which is responsible for reuptake of dopamine from the synaptic cleft into presynaptic terminals (Castellanos, 2001). Second, neuro-imaging studies of ADHD suggest changes in structure and function of brain regions rich in dopaminergic innervation (Spencer *et al.* 2005). Several studies have also shown increased DAT1 binding in ADHD (Dougherty *et al.* 1999; Dresel *et al.* 2000), although others have found lower DAT1 binding (van Dyck *et al.* 2002; Jucaite *et al.* 2005). Third, findings from animal studies have also implicated involvement of the dopaminergic system (Thapar *et al.* 2005*b*) and informed functional candidate gene studies of ADHD.

In summary, there has been evidence to support investigation of dopaminergic genes in ADHD. In this review, we focus on those genes for which association findings have been found to be significant in meta-analyses or pooled analyses or which are supported by at least two independent datasets. Detailed description of all candidate gene association findings in ADHD are provided elsewhere (Faraone *et al.* 2005).

Association findings for ADHD

The dopamine D4 receptor gene (*DRD4*)

Many studies have targeted the *DRD4* gene, which encodes the dopamine DRD4 receptor, and focused on a variable number tandem repeat (VNTR) polymorphism in which alleles differ by the number of repeats of a 48-bp sequence. The known size range varies from 2 repeats (2R) to 11 (11R). The allele containing 7 repeat units has now been extensively and convincingly implicated in ADHD, with at least four sets of published pooled or meta-analyses showing significant evidence for association (see Table 2). Reported odds ratios (ORs) from these studies have ranged from 1·13 [95% confidence interval (CI) 1·03–1·24] to 1·9 (95% CI 1·5–2·2). Although this finding is now strong and the variant is in a coding region (exon 3), how this variant influences disease risk at a mechanistic level is unclear (D'Souza & Craig, 2006).

The dopamine D5 receptor gene (*DRD5*)

A meta-analysis of five studies (Maher *et al.* 2002) and a larger international joint analysis of almost 2000 probands and 3000 of their parents from 14 research groups (Lowe *et al.* 2004) have shown significant association between ADHD and a repeat polymorphism in the *DRD5* gene. The associated polymorphism is based upon the number of copies of a two base repetitive sequence (a dinucleotide repeat), with the associated allele conferring a reported OR of 1·24 (95% CI 1·12–1·38, $p = 0{\cdot}00005$). A subsequent meta-analysis has also shown significant association with this variant (see Table 2) (Li *et al.* 2006). The associated polymorphism is, however, located 18·5 kb away from the protein encoding region of the gene and has no known function. Whether this polymorphism *per se* causes some alteration in the function of DRD5,

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Table 2. *Findings of pooled or meta-analyses studies of candidate gene findings for ADHD*

Gene	Study	Study design	No. studies included	Overall OR	95% CI	*p* value
DRD4 48bp VNTR	Faraone *et al.* 2001	Case–control	8	1·9	1·5–2·2	<0·001
	Faraone *et al.* 2001	Family-based	14	1·4	1·1–1·6	0·02
	Maher *et al.* 2002	Family-based	13	1·41	1·20–1·64	0·00002
	Faraone *et al.* 2005	Family-based	—	1·13	1·03–1·24	—
	Faraone *et al.* 2005	Case–control	—	1·45	1·27–1·65	—
	Li *et al.* 2006	Family and case–control	33	1·34	1·23–1·45	2×10^{-12}
DAT1 480bp VNTR	Purper-Ouakil *et al.* 2005	—	13	1·19	0·99–1·41	0·21
	Li *et al.* 2006	Family and case – control	23	1·04	0·98–1·11	0·20
	Maher *et al.* 2002	Family-based	11	1·27	0·99–1·62	0·06
	Curran *et al.* 2005	Family-based	9	1·15	—	0·06
	Faraone *et al.* 2005	Family-based	—	1·13	1·11–1·59	—
DRD5 148bp CA(n) microsatellite marker	Li *et al.* 2006	Family and case–control	9	1·34	1·21–1·50	8×10^{-8}
	Maher *et al.* 2002	Family-based	5	1·57	1·25–1·96	0·00008
	Lowe *et al.* 2004	Family-based	14	1·24	1·12–1·38	0·00005
COMT val^{158}met	Cheuk & Wong, 2006	Family and case–control	11	0·99	0·88–1·12	0·87
SNAP-25 (T1065G)	Faraone *et al.* 2005	Family-based	—	1·19	1·03–1·38	—
HTR1B (G861C)	Faraone *et al.* 2005	Family-based	—	1·44	1·14–1·83	—
Dopamine β-hydroxylase (*Taq*I)	Faraone *et al.* 2005	Case–control	—	1·33	1·11–1·59	—
5-HTTLPR	Faraone *et al.* 2005	Case–control	—	1·31	1·09–1·59	—
	Kent *et al.* 2002	Family-based	3	1·33	1·06–1·66	0·01

ADHD, Attention deficit hyperactivity disorder; OR, odds ratio; CI, confidence interval; —, data not given.

for example by influencing its abundance, or whether this association is indirect (that is the associated allele tends to be co-inherited with another polymorphism elsewhere in the gene, with the latter being functional) is unknown. Nevertheless, the evidence implicating *DRD5* in ADHD is now fairly robust.

The dopamine transporter gene (*SLC6A3*)

SLC6A3 (also known as *DAT1*) encodes the dopamine transporter (DAT1). Most published association studies of ADHD have focused on a VNTR in the 3′-UTR of the gene, a region of the gene that, while transcribed into mRNA, is not translated into protein. Data bearing on the question of whether or not this variant is functional are equivocal (D'Souza & Craig, 2006), as is the evidence for association. Indeed, five sets of published pooled and meta-analyses have yielded different findings. The first two sets of analyses (Maher *et al.* 2002; Curran *et al.* 2005), based on nine and 11 studies respectively (664 and 824 informative transmissions), showed evidence of heterogeneity across samples but only trends for association (OR 1·16, $p=0·063$ and OR 1·27, $p=0·06$). A more recent analysis based on an extended dataset found a small but significant association (OR 1·13, 95% CI 1·03–1·24) (Faraone *et al.* 2005). However, the two most recent pooled analyses (Table 2) have found no evidence for association (Purper-Ouakil *et al.* 2005; Li *et al.* 2006). Finally, in the largest study to date, the International Multicentre ADHD Gene (IMAGE) study, there was no evidence of association with the VNTR in the DAT1 3′-UTR (Brookes *et al.* 2006). It has been suggested that the lack of candidate gene association findings may be accounted for by site heterogeneity (Brookes *et al.* 2006). Thus, while possibly *a priori* the most compelling candidate gene, the evidence so far does not favour a role for DAT1 as a primary aetiological factor in ADHD. It should be stressed that even if it is not genetically associated, this does not refute the hypothesis of altered DAT1 function in ADHD as an important mediator in the pathophysiological cascade.

The synaptosomal associated protein (SNAP-25) *gene*

Interest in this gene has come from animal research. The coloboma mouse mutant, which has

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a chromosomal deletion containing *SNAP-25*, shows marked motor hyperactivity that is alleviated by stimulant medication (D-amphetamine but not methylphenidate). The hyperactivity is also ameliorated in coloboma mice modified to express *SNAP-25* (Hess *et al*. 1996). However, the relationship between *SNAP-25* and hyperactivity is not straightforward. *SNAP-25*-only knock-out mice (i.e. mice with no *SNAP-25* but with the additional genes in the coloboma deletion retained) are not hyperactive (Washbourne *et al*. 2002). These observations suggest that in the coloboma mice, low *SNAP-25* is necessary but not sufficient for the phenotype, and that deletion of another gene is likely to be contributory. In humans, evidence for association between *SNAP-25* and ADHD is still not fully convincing, as groups have studied different markers (Barr *et al*. 2000; Brophy *et al*. 2002; Mill *et al*. 2002; Kustanovich *et al*. 2003) and detailed studies are only beginning to emerge (Mill *et al*. 2004).

The serotonin transporter gene (*SLC6A4*)

Interest in the serotonergic system has again come from animal studies as well as some pharmacological studies. Although other variants have also been studied, independent replicated association findings have been reported for a functional variant in *SLC6A4*, the serotonin transporter gene. This is a 44-bp insertion/deletion polymorphism (usually referred to as 5-HTTLPR) in the promoter region of the gene. There are long and short allelic variants, with the short form being associated with lower transporter expression (Lesch *et al*. 1996), as well as reduced serotonin uptake in platelets (Greenberg *et al*. 1999). Pooled analysis (Kent *et al*. 2002) of data from three published studies (Manor *et al*. 2001; Seeger *et al*. 2001; Kent *et al*. 2002) showed an increased frequency of the long, higher-expression allele in children with ADHD and over-representation of the long/long genotype (OR 1·33, 95% CI 0·11–1·66, $p=0·01$) (Kent *et al*. 2002) (see Table 2). This finding has since been replicated in two case–control studies (Zoroglu *et al*. 2002; Beitchman *et al*. 2003) and two population-based studies that have examined subclinical symptoms related to ADHD (Retz *et al*. 2002; Curran *et al*. 2005). Studies across a variety of ethnic populations have, however, failed to find evidence of association (Langley *et al*. 2003; Kim *et al*. 2005; Xu *et al*. 2005; Banerjee *et al*. 2006; Heiser *et al*. 2006). A pooled analysis of case–control studies found significant association between the variant and ADHD (Faraone *et al*. 2005) (see Table 2), although as this did not include family-based studies or the most recent findings, perhaps this association requires further investigation.

Gene–phenotype links and intermediate phenotypes in molecular genetic studies of ADHD

ADHD, in common with other complex disorders, is generally considered to be both clinically and aetiologically heterogeneous. In other words it can show marked variation in clinical manifestation and this could reflect different risk factors operating through a variety of risk mechanisms. This has fuelled interest in a number of related molecular genetic research areas.

First, there has been research on whether different ways of categorically defining the ADHD phenotype (e.g. ADHD plus conduct disorder, ADHD subtypes) might index underlying aetiological heterogeneity (see Thapar *et al*. 2006 for a recent review). Second, there have been attempts to identify susceptibility genes for ADHD defined as a clinically quantitative trait, using population quantitative trait loci (QTL) genetic studies, rather than as a diagnostic category (Curran *et al*. 2005). Third, there is increasing interest in whether genetic variants that influence ADHD susceptibility also influence its clinical variability, including the developmental course (Thapar *et al*. 2007). Fourth, in line with genetics research across psychiatry, there has been increasing focus on potential intermediate phenotypes that lie on the pathway from risk factor to disorder (Doyle *et al*. 2005). Some researchers believe that identifying susceptibility genes for such intermediate phenotypes may prove more fruitful than focusing on psychiatric disorder. This type of research may also shed light on the mechanisms that mediate the link between specific risk factors and disorder. In the context of ADHD, this has mostly concerned neurocognitive intermediate phenotypes (Castellanos & Tannock, 2002), notably impairments in executive function, response inhibition and working memory.

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More recent attention has turned to imaging genomics (Meyer-Lindenberg & Weinberger, 2006), the goal of which is to determine how variations in brain structure or function might mediate the effects of genes on clinical disorder. However, imaging genetics is still in its infancy, at least with respect to ADHD, and very little is known about the links between genes, brain structure/function and the disorder, although some promising imaging intermediate phenotypes have been reported (Durston *et al*. 2005; see Seidman *et al*. 2005 for a recent review). We next focus on findings of links between replicated gene variants and specific phenotypic aspects of ADHD.

Dimensional measures of ADHD

The strength of evidence from twin studies that ADHD is heritable has mainly been based on dimensional measures of ADHD, but despite this, the associations between *DRD4*, *DAT1*, *DRD5* and *SNAP-25* and ADHD appear to be weaker when dimensional phenotypes are used rather than the clinical category (Mill *et al*. 2005). Although it is not yet clear whether this has arisen because there have been few molecular genetic studies based on quantitative measures of ADHD, the results to date suggest that, at least for these gene variants, the DSM-IV clinical phenotype of ADHD, despite its problems, has been most useful. However, this is not to say that it is the optimal phenotype definition for all purposes.

ADHD subtypes

To date, findings of links between specific gene variants and different ADHD subtypes have not been robust. Although not replicated, the first large, international pooled analysis of the *DRD5* variant showed association with a specific clinical phenotype, in that there was evidence of stronger association with the inattentive type of ADHD (Lowe *et al*. 2004). This finding, however, requires replication before conclusions can be drawn.

Developmental course of ADHD

Although twin studies have suggested that genetic factors account for continuity of ADHD symptoms over time, there have been very few longitudinal molecular genetic studies of ADHD. The evidence so far suggests that the DRD4 7-repeat allele appears to influence the course of ADHD, with two longitudinal studies (El-Faddagh *et al*. 2004; Langley *et al*. 2006) showing evidence of association with ADHD persistence over time but one published study failing to replicate this finding (Barkley *et al*. 2006). Finally, in the large Dunedin cohort sample, among those with ADHD, DRD4 and DAT1 gene variants not only predicted poor adult prognosis but were also associated with intellectual functioning indexed by IQ test scores (Mill *et al*. 2006).

Co-morbid conduct disorder

There have been a number of studies testing for association between a specific gene variant in catechol-*O*-methyltransferase (COMT) and conduct disorder symptoms in ADHD. COMT is an enzyme that metabolizes catecholamines and is involved the primary mechanism for dopamine clearance in the prefrontal cortex (PFC), which is relatively devoid of DAT1. There has been considerable interest in a polymorphism (val158met) in *COMT* that encodes a valine (val) to methionine (met) amino acid change. In brain, COMT with the val allele is around 40% more active than COMT with the met allele (Chen *et al*. 2004). Possession of the val allele is also associated with increased PFC dopamine clearance and worse performance on neurocognitive tasks assessing PFC function (Diamond *et al*. 2004; Meyer-Lindenberg *et al*. 2005), which might implicate this variant in the development of ADHD. However, meta-analysis provides no support for an association between val158met and ADHD (Cheuk & Wong, 2006).

Conversely, there is evidence that possession of the val allele is associated with conduct disorder symptoms/antisocial behaviour in ADHD (Thapar *et al*. 2005*a*). This finding has since been replicated in two independent population-based samples from the UK and New Zealand (Caspi *et al*. in press) but not in a Canadian sample (Joober & Sengupta, 2006). This finding is of interest in that it illustrates that some risk factors (here a functional COMT variant) may have modifying effects on the ADHD phenotype (here antisocial behaviour) but not increase risk for the disorder itself, at least with effect sizes of a magnitude that can be detected in sample sizes available to date.

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Cognitive phenotype

Although there has been much interest in neurocognitive measures in ADHD, there are no consistently replicated genetic findings. There have been some reports suggesting that the *DRD4* VNTR influences measures of cognitive functioning in ADHD (Swanson *et al.* 2000; Langley *et al.* 2004; Bellgrove *et al.* 2005; Mill *et al.* 2006) but, to date, different research groups have used different measures. Some have found that those possessing the *DRD4* 7-repeat allele perform more poorly on measures of accuracy, impulsiveness and general cognitive ability (Langley *et al.* 2004; Mill *et al.* 2006), whereas others find that those carrying the non-risk alleles have more cognitive deficits (Swanson *et al.* 2000; Bellgrove *et al.* 2005). Thus findings here have been mixed with no consistent patterns yet emerging.

Gene–environment interaction

The aetiology of ADHD, like all complex disorders, is not entirely explained by genes; environmental factors also contribute. Not all individuals exposed to environmental risk factors develop disorder; that is, individuals differ in their response to specific environmental factors. Equally, for complex diseases, not all individuals carrying susceptibility gene variants will develop the disorder unless they are exposed to environmental risk factors. This phenomenon of gene–environment interaction is now being increasingly recognized as an important contributor to complex diseases and behaviour and may contribute to non-replication across molecular genetic studies (Moffitt *et al.* 2005; Rutter *et al.* 2006).

Studies of gene–environment interaction in ADHD are at an early stage so there is, as yet, no large body of replication data from which to draw robust conclusions. The following reports should therefore be taken as indicative of the direction of investigation, rather than confirmed findings. In one association study of a non-clinical US sample, the *DAT1* 148-bp allelic variant was shown to be associated with hyperactive-impulsive symptom scores only in those who were exposed to maternal smoking in pregnancy (Kahn *et al.* 2003). Subsequently, another study also found evidence of interaction between prenatal smoking exposure and DRD4 and DAT1 gene variants in increasing the risk of DSM-IV ADHD, although in this study the interaction was with a different allele of the DAT1 variant (Neuman *et al.* 2006). However, these findings have not been replicated in a clinically referred sample (Langley *et al.* in press). In a recent study of ADHD, there was evidence that those carrying a previously unstudied haplotype combination of markers in the *DAT1* gene were more sensitive to prenatal exposure to alcohol (Brookes *et al.* 2006). There have also been two studies investigating interaction between the *DRD4* 7-repeat allele and the season of birth (Seeger *et al.* 2004; K. Brookes *et al.* unpublished observations). However, results from these studies differed from each other. Finally, in a study from our own group, there was evidence to suggest that those with ADHD possessing the *COMT val/val* genotype were more sensitive to the adverse effects of a lower birthweight and those exposed to both risk factors showed higher conduct disorder symptoms (Thapar *et al.* 2005*a*).

Pharmacogenetics represents a type of gene–environment interaction that may eventually impact on clinical practice. Pharmacogenetic studies aim to identify genetic variants that influence clinical response to medication. Although there have a few studies investigating gene variants in children with ADHD that predict clinical response to ADHD (McGough, 2005), such studies are at an early stage and robust findings have yet to emerge.

Conclusions

Genetics research on ADHD is progressing very rapidly at an international level. Family, twin and adoption study findings have been highly consistent in showing a strong genetic influence on ADHD. These studies also suggest that genetic influences contribute to the overlap between ADHD and conduct disorder and to ADHD persistence.

A number of robustly replicated molecular genetic findings have withstood analyses by means of pooled and meta-analyses. To date, all of the associated gene variants have been of small effect and in the future there will be increasing interest in examining the risk effects of multiple genes (gene–gene interaction) and interaction with environmental risk factors.

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Larger-scale genetic studies based on much bigger sample sizes achieved through international collaboration are likely to result in the identification of further ADHD susceptibility genes. Investigation of gene–clinical phenotype links is important and replicated findings so far suggest that examining these relationships will be fruitful. As in all epidemiology, identifying an associated factor is just the starting point for investigating whether it has a causal risk effect. The real challenge, but also the excitement, lies in identifying causal pathways and mechanisms. Success in these areas will enable the identification of biological targets and pathways for new medications as well as inform appropriate methods of risk reduction and treatment through environmental means.

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DECLARATION OF INTEREST

None.

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