Unravelling the complexity of attention-deficit hyperactivity disorder: a behavioural genomic approach*

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Summary International research has established that there is a strong genetically inherited contribution to attention-deficit hyperactivity disorder (ADHD) and the genetic mechanisms involved are being sought with considerable success. It is now established that certain alleles of the genes coding for the dopamine D_4 receptor and the dopamine transporter occur more frequently in children with ADHD than in healthy controls, and we are finding other DNA changes associated with ADHD. A major challenge for the field now is to clarify how genetic susceptibility is translated into disorder by integrating the fields of quantitative and molecular genetics, neuropsychology and environmental risks.

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Attention-deficit hyperactivity disorder (ADHD) is a common, highly heritable neurodevelopmental disorder affecting 3–4% of children and 1% of adults. The disorder starts in early childhood and is characterised by pervasive behavioural inattention, hyperactivity and impulsivity that is inappropriate to the developmental stage. Symptoms persist into adult life in the majority of cases either as the operationally defined disorder or persistence of some symptoms associated with academic, occupational and social impairments. The trait-like characteristic of ADHD symptoms that start in early childhood and have a chronic persistent course, and the frequent concurrence of symptoms such as mood instability alongside 'core' ADHD symptoms, lead to frequent misspecification of the diagnosis in adults. The disorder is associated with increased risk of several child, adolescent and adult psychiatric disorders, including drug and alcohol misuse, antisocial behaviour, anxiety, depression, and general and specific learning difficulties. Recognition and appropriate treatment of ADHD in all age groups is therefore of considerable importance (Faraone *et al*, 2000*b*; Taylor *et al*, 2004).

QUANTITATIVE GENETIC STUDIES

Although ADHD is clinically heterogeneous, quantitative genetic studies are helping to unravel its complexities. Genetic research started with the recognition by Morrison & Stewart (1971) and Cantwell (1972) that hyperactivity aggregates in families. More recent studies estimate a four- to eight-fold increase in risk for ADHD among first-degree relatives of ADHD probands compared with the general population risk (Faraone *et al*, 2000*a*; Willcutt, 2005). Numerous twin studies demonstrate that familial segregation is influenced by genetic factors with heritability estimates in the range 60–90% (Thapar *et al*, 1999). Twin studies support conceptualisation of ADHD as the extreme of a continuously distributed trait, with genetic risk distributed throughout the population.

Our quantitative genetic studies have moved beyond simple estimations of heritability to answer more complex questions about genetic and environmental influences on course and development. Analysis of ADHD symptoms in the Twins Early Development Study found that stability of ADHD symptoms from age 2 years to 8 years is accounted for mainly by shared genetic influences (Kuntsi *et al*, 2005). Whether the genes associated with ADHD in childhood are the same as those associated with the disorder in adults is an empirical question that has not yet been answered.

Shared genetic factors also explain familial associations between ADHD and comorbid disorders and traits including conduct disorder, dyslexia and lower IQ. The recognition of shared genetic influences is conceptually important, suggesting the existence of multiple overlapping (pleiotropic) effects of genes, rather than heterogeneous influences where individual sets of genes map onto individual developmental pathways. Pleiotropy is in fact expected, since most genes that regulate brain function are expressed in multiple brain regions and functional genetic variation will therefore affect more than one neuronal pathway or system. Shared genetic effects may also indicate developmental trajectories whereby genes influence disorder A (e.g. ADHD) which in turn increases risk of disorder B (e.g. antisocial behaviour). Detecting the specific genes involved will help to clarify the causal relationships between ADHD and co-occurring disorders and traits.

MOLECULAR GENETIC STUDIES

Molecular genetic studies have developed rapidly since the first reports of association with the dopamine D_4 receptor and dopamine transporter gene (*DAT1*). These findings have stood the test of time with multiple replications (and non-replications) and evidence from meta-analyses confirming small but significant effects on risk for ADHD. Our analysis, and that of others, suggests the involvement of other dopamine pathway genes including the dopamine D_5 receptor and a synaptosomal-associated protein (SNAP-25) involved in vesicular release of neurotransmitters. Genes with evidence suggesting association but requiring more extensive analysis include dopamine α-hydroxylase, serotonin 1B receptor, serotonin transporter, β_4-nicotinic

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receptor subunit, noradrenergic transporter gene and brain-derived neurotrophic factor (reviewed in Asherson & the Image Consortium, 2004).

Linkage studies using affected sibling pairs and extended pedigrees have identified several chromosomal regions containing putative ADHD susceptibility genes. These are not yet confirmed by identification of specific genes, but seem to identify larger influences than the candidate gene associations and have the potential to identify novel genes and developmental processes. Chromosomal regions highlighted by replication across studies or accumulating evidence with increasing sample size include chromosomes 5p13, 6q12, 16p13 and 17p11. A further sib-pair linkage study, the International Multicentre ADHD Genetics (IMAGE) Project, will provide additional linkage data in the coming year (Asherson & the Image Consortium, 2004). Several of these loci overlap with those highlighted in studies of other developmental disorders, in particular autism (5p13, 16p13 and 17p11). Whether the same genes are involved will become clear when specific genes are identified.

ENVIRONMENTAL RISK FACTORS

As in other areas of psychiatry, the nature *v.* nurture debate on ADHD has been vociferous over the years. Environmental risks for ADHD were known before genetic influences were established. Still (1902) first reported a hyperactive behaviour pattern occurring when brain damage was expected but could not be demonstrated, and this was postulated to include factors such as birth injury or mild anoxia. This laid the foundation for the concept of minimal brain damage/dysfunction, a childhood syndrome that included developmental impairments in control of attention, impulse and motor function as well as perception, conceptualisation, language and memory linked to deviations in the function of the central nervous system. The subsequent finding that genetic factors explain familial aggregation of ADHD suggested a likely role for gene–environment interaction (Rutter & Silberg, 2002).

Three main groups of environmental risk factors have been identified. The first group comprises prenatal and perinatal events, such as prematurity, low birth weight, pregnancy and/or birth complications and mother's use of alcohol or tobacco during pregnancy. The second consists of parental and family factors such as early and severe neglect, and later influences upon the course such as critical expressed emotion *v.* expressed warmth, inconsistent parenting, parental divorce, family conflict and early institutional rearing. The third group comprises acquired neurobiological risks such as closed head trauma and exposure to lead (reviewed by Kuntsi & Asherson, 2004). Further research is needed to determine which of these:

(a) are proximal risks affecting the brain directly (e.g. toxicity from alcohol);

(b) act indirectly (e.g. maternal drinking correlates with poor parenting, and poor parenting is a proximal risk);

(c) are genetically correlated with the genotype of the mother (e.g. mothers with ADHD are more prone to smoke during pregnancy than mothers without ADHD);

(d) are genetically correlated with ADHD proband genotype (e.g. ADHD behaviour evokes hostile expressed emotion in the parent).

To date, only a few molecular genetic studies of ADHD incorporate environmental risk measures. Kahn *et al* (2003) reported that in pre-school children, hyperactivity–impulsivity and oppositional behaviour were associated with genetic variation of *DAT1* but only in a group exposed to maternal smoking during the pregnancy. More recently we found that the *DAT1* association with ADHD was confined to a group whose mothers had drunk alcohol during pregnancy. These studies suggest that functional variation of the *DAT1* gene modifies the direct effects of tobacco and alcohol on the developing foetal brain and thereby risk for ADHD. Although this is a plausible neurobiological hypothesis, these data are equally consistent with the influence of damaging parental influences, since we know that mothers who smoke during pregnancy are more likely to be antisocial, have children with antisocial men, bring up their children in disadvantaged circumstances and to be depressed (Maughan *et al*, 2004). Although some studies report that risk from prenatal exposure to alcohol and tobacco is not accounted for by parental ADHD or antisocial behaviour, further studies are needed to identify the direct causal factor.

NEUROCOGNITIVE PROCESSES

A major challenge arising from the success of genetic research is to identify the neurocognitive processes that mediate genetic influences on ADHD. Although much progress has been made in cognitive-experimental research on ADHD a consensus is yet to emerge on the key underlying processes. Interpretation of neurocognitive data is complex, with alternative explanations for poor performance on experimental tasks including impaired ability to withhold a response, deficient extinction processes, attentional problems, insufficient ability to regulate the state of activation, altered motivational processes and working memory impairments (Castellanos & Tannock, 2002; Kuntsi & Asherson, 2004). Part of the difficulty in specifying the cognitive processes relates to the inconsistency that often characterises performance of children with ADHD. Within-task manipulations with variables such as incentives or presentation rate often influence whether or not a cognitive 'deficit' is observed. Thus, although many authors have attempted to formulate a single neurocognitive theory of ADHD, it is often not clear what neurocognitive processes underlie performance on a particular cognitive experimental task.

Quantitative genetic analyses have the potential to narrow the focus to one or more causal pathways. We can investigate the extent to which cognitive experimental measures that tag 'distinct' neurocognitive processes correlate with each other and with ADHD behaviours and the extent to which shared genetic influences account for such correlations. We might, for example, expect to see multiple overlapping effects of genes on neurocognitive processes implicated in ADHD. It currently remains a matter of conjecture whether the various psychological constructs put forward to explain ADHD have the same or different underlying cause or causes. Kuntsi & Stevenson (2001) were the first to apply a genetic design to identify cognitive processes that mediate genetic influences on ADHD, and we are currently engaged in further family and twin studies to provide empirical answers to these questions. Molecular genetic studies investigating attention and response inhibition have also been completed, but no firm conclusion can yet be drawn owing to small sample sizes and inconsistency across data-sets. Another

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strand of our research is the use of family and twin designs to investigate genetic and environmental influences on brain structure and function. Neuroimaging studies have identified structural and functional changes in the prefrontal cortex, striatum and cerebellum as well as evidence for increased dopamine transporter density in the striatum, but as yet little is known about their relationship to individual differences in the risk for ADHD (Castellanos & Tannock, 2002; Kuntsi & Asherson, 2004).

CONCLUSIONS

The new genetics was heralded by the near completion of the human genome sequence and has been followed by a rapid rise in the number of identified genetic variants. It has shifted the goal of behavioural genetic research from gene discovery towards gene functionality (McGuffin & Plomin, 2004). Quantitative genetic findings have shifted perception of ADHD towards that of a quantitative trait sharing aetiological influences with other developmental, behavioural and cognitive traits. Molecular genetics has confirmed *a priori* hypotheses of dopamine system dysregulation and promises to identify additional genes in the coming decade. Combining genetic, environmental and neurobiological research has the potential to delineate causal links between ADHD and the developmental course of the disorder, including persistence of ADHD symptoms into adulthood and comorbidity with associated psychiatric disorders and traits. At a time when the role of developmental disorders is increasingly recognised within adult as well as child psychiatry, the accruing knowledge holds promise for the development of new clinical approaches to previously intractable problems.

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