

# Characterizing the ADHD phenotype for genetic studies

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## Abstract

*The genetic study of ADHD has made considerable progress. Further developments in the field will be reliant in part on identifying the most appropriate phenotypes for genetic analysis. The use of both categorical and dimensional measures of symptoms related to ADHD has been productive. The use of multiple reporters is a valuable feature of the characterization of psychopathology in children. It is argued that the use of aggregated measures to characterize the ADHD phenotype, particularly to establish its pervasiveness, is desirable. The recognition of the multiple comorbidities of ADHD can help to isolate more specific genetic influences. In relation to both reading disability and conduct disorder there is evidence that genes may be involved in the comorbid condition that are different from pure ADHD. To date, progress with the investigation of endophenotypes for ADHD has been disappointing. It is suggested that extending such studies beyond cognitive underpinnings to include physiological and metabolic markers might facilitate progress.*

## Introduction

The genetic study of ADHD has made more progress than that of other behavioural and neurodevelopmental disorders. ADHD is often found to be comorbid with reading disability, which, in turn, is the disorder of cognition where most progress has been made in understanding the genetic basis (Fisher & DeFries, 2002). For this reason, the study of the genetics of ADHD has a special relevance in guiding the investigation of the genetic basis of other forms of behavioural and neurodevelopmental disorders. This paper will consider progress in the investigation of genetic factors in ADHD, in its comorbidities, and will summarize the features characterizing the ADHD phenotype that are most valuable for genetic studies.

## Progress with genetics of ADHD

It has become apparent from studies conducted over the last 10 years that ADHD is a condition in which genetic

differences between children make a substantial contribution to the risk of the disorder. These studies were initially concerned with demonstrating that the heritability of the condition was high. Heritability is the proportion of the causal factors on a characteristic that is attributable to genetic differences between children. More recent research has centred on the question of which particular genes may be involved in ADHD (Todd, 2000). From such studies it has become clear that ADHD is one of the most strongly genetically influenced of the common behavioural disturbances seen in children (Swanson *et al.*, 2001). As a consequence of the progress that has been made in studying genetic influences on ADHD, it now represents a model for the study of other childhood disorders. Indeed, the study of ADHD represents a good example of the suggested stages in the study of behavioural phenotypes put forward by Martin, Boomsma and Machin (1997). They proposed that the study of any behavioural characteristic where genetic factors were thought to be important should go through five overlapping stages. The first of these is to demonstrate the plausibility of the role of genetic factors. Evidence

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that is consistent with genes being important comes, for example, from the demonstration of a family history. If either brothers and sisters show the condition or parents report that they themselves showed the condition in childhood, then this is necessary, but not sufficient, evidence for the role of genetic factors. For ADHD, such familiarity has been demonstrated in a series of studies by Biederman and colleagues (1992).

The second stage is to develop a psychological theory about the phenotype in question. There have been a number of such theories for ADHD, including explanations in terms of deficits in behavioural inhibition (Barkley, 1997) and delay aversion (Sonuga-Barke, 2002). A more comprehensive account of the relationship between psychological theories and genetic research can be found in Kuntsi and Stevenson (2000).

The third stage is to identify the extent of genetic and environmental influences on the underlying processes contributing to the condition. There have been many twin studies that have replicated the initial demonstration by Goodman and Stevenson (1989) of a pattern of substantial genetic plus non-shared but no shared environmental influences on hyperactivity (see Faraone & Doyle, 2001, for review).

Once such studies have demonstrated that genetic factors do indeed contribute significantly to the condition, there is justification for moving on to the fourth stage, which is to use the methods of molecular genetics to attempt to locate the genes that are involved. There is a range of such molecular genetic techniques but it is beyond the scope of this paper to describe these in detail. A good account of these is given in Craig and McClay (2003). These techniques broadly divide into those concerned with linkage, by which the coinheritance of a condition and a gene or genetic marker is investigated through successive generations in the family, and association studies, in which, within the population, the frequency of a gene or a genetic marker is shown to be increased in those with a condition compared to an appropriate control or comparison group. The number of molecular genetic studies of ADHD has expanded greatly and includes both linkage approaches (e.g. Fisher *et al.*, 2002) and association studies of candidate genes (e.g. Daly, Hawi, Fitzgerald & Gill, 1999).

The fifth and final stage in this sequence prescribed by Martin, Boomsma and Machin (1997) is the study of the natural history of the expression of genetic and environmental risk factors. These studies can be undertaken with much greater power once the genes involved have been established. Molecular genetic studies of ADHD have provided replicated evidence of the involvement of genes influencing the functioning of the dopamine system and, in particular, of the dopamine receptor D4 gene (DRD4). Faraone, Doyle, Mick and Biederman (2001)

have undertaken a meta-analysis of the evidence implicating the 7-repeat allele form of DRD4 in ADHD.

This evidence now justifies studies of individuals carrying the risk version of the gene to investigate how this acts alongside environmental risk factors to influence the phenotype. These studies can address questions of whether there is evidence of additive effects, where genetic and environmental risk factors contribute cumulatively to the condition, or whether there is evidence of moderating effects, whereby a child with a risk version of the gene may experience certain environments or experiences that reduce the likelihood that this genetic risk will be expressed. There is less consensus on which environmental influences might be included in such studies, although there is replicated evidence that care in institutions (e.g. Roy, Rutter & Pickles, 2000), prematurity (Saigal, Pinelli, Hoult, Kim & Boyle, 2003) and food additives (Bateman *et al.*, 2004) all play a role.

Although the study of ADHD has not moved through all five of these stages in a comprehensive way, progress has been made. Further progress is going to depend in part on the question of just what is the appropriate phenotype to investigate. There needs to be interplay between the investigation of genetic influences on ADHD and studies of the behaviour and cognitive characteristics of the condition. In the absence of such interplay, attempts to identify genes responsible for the range of behaviours associated with ADHD will be hampered by operating with clinically defined characteristics that may be complex and less amenable to genetic investigation. Equally, the findings from genetic studies can inform the refinement of the phenotype by identifying features that may reflect a common genetic influence and distinguish these from others that may be more environmentally determined or that are influenced by other genetic mechanisms. By these means, genetic studies can help to identify the sub-components of this complex set of behaviours. Consideration will be given now to the progress in refining the ADHD phenotype for genetic analyses and the implications this research has for understanding how the ADHD phenotype should be characterized.

### **Genetics and diagnostic classificatory frameworks versus dimensional approaches**

The Australian twin studies have provided findings that address the question of whether existing classificatory frameworks, such as DSM-IV, are appropriate for defining phenotypes for genetic studies. Analyses of the data from the Australian Twin ADHD Project suggest that there is evidence that different types of ADHD tend to breed true, that is, ADHD is transmitted in the same form

across generations. This was shown for the Predominantly Inattentive, Predominantly Hyperactive-Impulsive and combined sub-types in the DSM-IV classification (Levy, McStephen & Hay, 2001). These analyses have been based both on patterns of genetic effects on symptoms of ADHD and on concordances for categories based on DSM-III-R/DSM-IV classifications and latent class analyses (Rasmussen, Neuman, Heath, Levy, Hay & Todd, 2004).

The DeFries and Fulker (DF) analysis addresses this same question in a different manner (DeFries & Fulker, 1985). Here, probands are identified as being on the extreme end of a continuum of symptom severity. Using data from twin samples, the differential regression to the mean of the co-twins of monozygotic and dizygotic probands can be used to estimate the magnitude of the genetic effects contributing to proband status. If the estimate of group heritability does not change as more extreme definitions of probands are used, then there is *prima facie* evidence that a continuum model is appropriate. That is, as more extreme degrees of symptom severity are investigated, the relative magnitude of genetic and environmental influences is not changed. This is consistent with ADHD being on a continuum of severity spreading into the normal range.

There have been a number of studies that have adopted this DF method to test the validity of a continuum approach to the study of the genetics of ADHD (Gjone, Stevenson & Sundet, 1996; Levy, Hay, McStephen, Wood & Waldman, 1997). There is no consistent evidence to suggest that as more extreme probands are identified that group heritability changes. These findings suggest that genetic methods based upon continuously varying traits (such as quantitative trait locus analysis, Sham, 2003) are well suited for investigating the genetics of ADHD symptomatology.

### Ratings by single and multiple reporters

Quantitative approaches to measuring the ADHD phenotype are frequently reliant on reports and ratings by parents and teachers. There is often only modest agreement between the ratings obtained from these two sources. This could arise because ADHD behaviour is situation specific or because of rater biases. Anita Thapar has produced the following discussion of the impact of using single reporter and consensus ratings of ADHD symptoms from two sources on both quantitative and molecular genetic analyses. In genetic studies there are a number of options for the way multiple reporter information can be used to characterize the phenotype. These include the analysis in parallel of phenotypes defined by separate reporters (mother, father, teachers, self or other reports), the use of an aggregate composite to define a pervasive phenotype, or the use

of multivariate statistics to identify latent variables or classes. The adoption of these approaches in genetically informative designs can also aid the development of classification and diagnostic procedures.

A feature of parent reports in a large number of twin studies is typically that of high monozygotic correlations (0.60 to 0.90) and low dizygotic correlations (0.11 to 0.49). Indeed, with some measures, negative dizygotic correlations are found. These low or negative dizygotic correlations could arise either as a result of sibling interactions or from rater contrast effects. Quantitative genetic analyses suggest the latter is the most likely explanation (Simonoff, Pickles, Hervas, Silberg, Rutter & Eaves, 1998). The situation is different with teacher's ratings where contrast effects are not found. Here, heritabilities are somewhat lower and evidence of shared environmental effects emerge. The pattern of results appears different again when self-reports are analysed within a twin study framework. In these studies, heritability is even lower and non-shared environmental effects (including error variance) predominate with some shared environmental influence. When teacher and parent reports are analysed together in a bivariate analysis, common genetic influences are detected. The analysis of an aggregated pervasive definition of the phenotype has the advantage of corresponding more closely to the clinical definition of the condition. The heritabilities of pervasively defined ADHD are high (around 0.80) and there is no evidence of contrast effects.

The use of multiple reporters in molecular genetic studies is less extensively investigated. These are nearly all based on DSM-IV ADHD or ICD-10 Hyperkinetic Disorder definitions. However, association of the DRD4 7-repeat allele has been found with clinical and dimensional (mothers ratings) studies. Thapar and colleagues have undertaken a reanalysis of data showing that the presence of the DRD4 7 allele predicts parent-rated ADHD ( $\beta = 0.20, p < .05$ ) but not teacher-rated ADHD ( $\beta = -.04, n.s.$ ). These results and those of previous studies suggest that the use of multiple informants is a sensible approach to phenotype definition, with particular value coming from definitions based on pervasiveness. The use of statistical techniques to identify latent variables and/or latent classes from multiple informant data may be particularly advantageous in both quantitative and molecular genetic studies of ADHD.

### Genetic analysis of comorbidities of ADHD

The study of the genetics of ADHD has to address the problem of the extensive comorbidities between ADHD and other behavioural and cognitive disorders. There are a number of genetically informative studies that have

addressed the question of how the association between ADHD and reading disability (RD) might arise. Initial studies of ADHD (Smalley, 1997) and RD (DeFries, Fulker & LaBuda, 1987) in isolation have shown that both are substantially influenced by genetic differences between individuals. The clear conclusion from subsequent studies investigating their co-occurrence is that there is a common genetic aetiology (Stevenson, Pennington, Gilger, DeFries & Gillis, 1993; Light, Pennington, Gilger & DeFries, 1995; Willcutt, Pennington & DeFries, 2000). This raises the possibility either that RD and ADHD in general are influenced by the same genes, or that when they co-occur this comorbid group have a distinct genetic origin from those acting on RD and ADHD in isolation. Based on the finding that comorbidity between reading disability and ADHD is due to common genetic influences, the well-replicated quantitative trait locus (QTL) for reading disability on chromosome 6p was examined by Willcutt and colleagues to establish if it is also associated with increased susceptibility to ADHD. Significant linkage of ADHD to several DNA markers in this region was found. Moreover, significant bivariate linkage was obtained for ADHD and four measures of reading difficulty, suggesting that comorbidity between RD and ADHD is due, at least in part, to this QTL. These results provide the first evidence for a QTL that effects two complex psychological disorders, and suggest that this may provide a powerful approach for future studies of the etiology of ADHD and its comorbidity with other disorders. It has been found that there is some evidence of linkage between reading disability and locus near to the DRD4 gene at 11p15.5 (Hsuang, Kaplan, Petryshen, Lu & Field, 2004). It is important to note that this study did not find an association between reading disability and the 7-repeat allele of DRD4, which is associated with ADHD.

### Molecular genetic fractionation of the ADHD phenotype

A number of genes have been suggested as being implicated in ADHD. The largest group are those affecting the transmission at synapses including the serotonin transporter gene (5-HTTLPR) (e.g. Manor *et al.*, 2001), dopamine D4 receptor gene (DRD4) (e.g. see meta-analysis by Faraone *et al.*, 2001), dopamine transporter gene (DAT1) (e.g. Daly *et al.*, 1999), dopamine D5 receptor gene (DRD5) (e.g. Payton *et al.*, 2004) and SNAP-25 (e.g. Mill *et al.*, 2002; Mill *et al.*, 2004). This raises the question of how these genes combine to effect the risk of ADHD, for example, do they act additively or are certain combinations of risk alleles particularly potent?

There is also a question of whether different genes contribute to specific aspects of the ADHD phenotype, for example, do particular genes influence impulsivity and others play a greater role in inattention? Using a quantitative behaviour genetic analysis, Todd *et al.* (2001) have shown that the concordance for MZ pairs for the combined and inattentive types of DSM-IV ADHD are 83% compared to 69% for DZ. This indicates that the type of ADHD is transmissible and that genes play a role.

The best replicated association between a genetic polymorphism and ADHD is that for DRD4. Faraone *et al.* (2001) undertook a meta-analysis of case control and family-based association studies for the 7-repeat allele of the DRD4 gene. This showed a combined odds ratio for the case-control studies of 1.9 (CI 95% 1.5–2.2), with a slightly lower value for the family studies. There is some suggestion that the association with the 7-repeat allele may be stronger when ADHD is combined with conduct disorder (CD). Holmes *et al.* (2002) used a transmission disequilibrium test with ADHD plus CD cases and controls, and found the allele-specific test for the transmission of the 7-repeat allele was significant at  $p < .05$ . This accords with previous quantitative genetic family (Faraone, Biederman, Mennin, Russell & Tsang 1998) and twin studies (Thapar *et al.*, 2001), which show a higher familial risk and heritability for comorbid ADHD and CD. Therefore, it may be that variation in the DRD4 gene is particularly implicated in the behavioural disinhibition element of the ADHD phenotype, at least in so far as this leads to conduct disorder.

Waldman (2003) has undertaken a meta-analysis of the studies on the DAT1 polymorphisms and ADHD subtypes. The results indicate that the DAT1 polymorphism is more closely associated with the combined sub-type than with the inattentive sub-type of ADHD. The data from 13 independent samples was pooled to test for the association between ADHD and a common 148-base-pair allele of a micro-satellite marker of the DRD5 gene (Lowe *et al.*, 2004). There was a significant association (odds ratio = 1.24). This was primarily with the predominantly inattentive and combined sub-types of ADHD.

The interest in molecular genetic studies provides an opportunity to directly investigate gene–environment interaction. A number of environmental factors are known to be related to ADHD, for example, low birth weight, drug, alcohol and cigarette exposure are all examples of pre- and peri-natal risk factors (Spencer, Biederman, Wilens & Faraone, 2002). The question then is, to what extent do environmental factors moderate genetic risks? As yet unpublished data from Mill and Asherson suggest that the effects of the DAT1 10-repeat allele are more marked when the child has been exposed to pre-natal alcohol (Mill *et al.*, 2004).

There is increasing evidence that SNAP-25 may influence ADHD through a genomic imprinting process. The transmission of risk of ADHD via this gene is primarily paternal (Brophy, Hawi, Kirley, Fitzgerald & Gill, 2002; Kustanovic, Merriman, McGough, McCracken, Smalley & Nelson, 2003; Mill *et al.*, 2004.). Our understanding of the molecular genetics of ADHD is that there are many genes involved and each has a small effect. However, it may be that some genes have a larger effect in certain sub-sets of the ADHD population. The latent class approach to this issue looks promising (Todd, Joyner, Ji, Sun, Reich & Neuman, 2004; Rasmussen *et al.*, 2004) Gene–gene interactions are likely to be found and there is evidence emerging of gene–environment interactions and of some epigenetic factors such as imprinting (Kirley *et al.*, 2002).

### How productive is the study of endophenotypes?

The final question to be addressed is whether it is fruitful to search for endophenotypes. These are characteristics, which, in the present context, mediate genetic influences on the phenotype (other endophenotypes may mediate experiential influences on the phenotype). For this approach to be of value it is likely that the endophenotype will be at least as heritable as the behavioural phenotype (ADHD symptomatology), but there is also some dissociation such that an individual may be extreme on the endophenotype but not show the behavioural phenotype (Nigg, Doyle, Wilcutt & Sonuga-Barke, in press). There have been some initial attempts to use quantitative genetic approaches to the examination of endophenotypes, one of which has indicated the significance of state-regulation as a mediator of genetic effects. For example, Kuntsi and Stevenson (2001), and Kuntsi, Oosterlaan and Stevenson (2001) have shown that a number of underlying cognitive and motivational factors are related to ADHD, but that of these, a measure of response time variability (an indicator of state-regulation deficits) was the most likely candidate as the endophenotype carrying genetic effects on ADHD behaviour.

Molecular genetic approaches have produced less clear results. These approaches include the comparison of cognitive abilities for individuals with different genotypes in terms of alleles shown to carry genetic risk of ADHD, for example, DRD4. Swanson *et al.* (2000) found that although the 7-repeat allele was consistently associated with the behavioural profile of ADHD, the measurement of endophenotypes was not. Indeed, in this case, the measures of the endophenotype used

(reaction times and reaction time variability) were normal in the ADHD children with the 7-repeat allele. An alternative approach is to use as endophenotypes metabolic and physiological markers of the ADHD phenotypes rather than cognitive characteristics. For example, Wigal *et al.* (2003) have shown that circulating catecholamines show a greater peak response to exercise in control than in treatment of naïve ADHD subjects. The possibility that the level these circulating catecholamines reflect that action of different genetic polymorphisms warrants further exploration.

### Concluding comments

The conclusions from this review of the characterization of the phenotype for genetic investigation of ADHD are that:

1. Quantitative approaches to measuring the behavioural ADHD phenotype are appropriate;
2. Multiple informant ratings of behaviour provide valuable pervasive measures of ADHD and higher heritabilities than single informant approaches;
3. Genetic studies of ADHD should investigate separately ADHD alone and ADHD plus RD cases.
4. As yet, there are only rudimentary insights into the value of using cognitive, motivational, metabolic or other indicators of possible endophenotypes.

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