

**The Etiology of ADHD:  
Behavioral and Molecular Genetic Approaches**

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## The Etiology of ADHD: Behavioral and Molecular Genetic Approaches

The past decade has produced an exponential increase in research examining the genetic and environmental factors that affect individual differences in attention and activity level, as well as clinically significant elevations of symptoms of attention-deficit/hyperactivity disorder (ADHD). This rapid accumulation of new knowledge illustrates the potential impact of behavioral and molecular genetic methods. However, results of these studies have also underscored the complexity of the etiological pathways to ADHD and other psychopathologies, and demonstrate clearly how much is yet to be learned.

Behavioral genetic studies have demonstrated conclusively that genetic influences play a role in the etiology of ADHD, as is true for virtually all psychological traits and disorders (e.g., Plomin, DeFries, McClearn, & McGuffin, 2001). Similarly, environmental factors also play an important role in the etiology of ADHD. Therefore, the question is no longer whether ADHD is due to nature or nurture. Instead, the focus of behavioral genetic studies has shifted to the identification of specific genetic and environmental factors which increase susceptibility to ADHD. These results will provide an essential tool to facilitate the development of comprehensive models describing the mechanisms through which these etiological factors affect brain development, and how these changes in the brain lead to the symptoms of ADHD.

I have four primary objectives in this chapter: (1) to summarize previous family and twin studies of ADHD; (2) to review the results of candidate gene and linkage studies of ADHD; (3) to discuss ways that behavioral and molecular genetic methods can be used to clarify issues of diagnostic nosology, and (d) to describe future research directions for the integration of behavioral and molecular genetic methods in studies of brain functioning. Before turning to these four objectives, I first describe briefly the current conceptualization of ADHD.

### The nature of ADHD and the importance of etiology

Few disorders have undergone as many changes in name and diagnostic criteria as ADHD, perhaps because few disorders have been the subject of as much taxonomic study. The most recent definition of ADHD in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994)* distinguishes among diagnostic subtypes characterized by maladaptive levels of both inattention and hyperactivity-impulsivity (combined type), maladaptive levels of inattention only (predominantly inattentive type), and maladaptive levels of hyperactivity-impulsivity alone (predominantly hyperactive-impulsive type).

Relatively few behavioral and molecular genetic studies have incorporated measures of *DSM-IV* ADHD, and many have assessed hyperactivity or inattention with rating scales that are not derived from *DSM* symptoms. Thus, while I emphasize studies of *DSM-IV* ADHD when sufficient data are available, I also review relevant studies that used other measures to provide the most complete account of the current state of knowledge regarding the etiology of ADHD.

### Behavioral genetic studies of ADHD

Individuals cannot be randomly assigned to different environmental or genetic backgrounds. Therefore, family, adoption, and twin studies take advantage of naturally occurring events to estimate the relative influence of genetic and environmental factors on a trait or disorder (for a detailed overview of these methods see Pennington, 2002 and Plomin et al., 2001). The influence of genes is quantified by estimating *heritability*, the proportion of the total phenotypic variance in a trait that is attributable to genetic influences. The proportion of variance due to environmental factors can be subdivided into *shared* and *nonshared environmental influences*. Shared environmental influences are those that increase the similarity of individuals within a family in comparison to unrelated individuals in the population. In contrast, nonshared environmental influences are those that lead to differences among individuals in a family. In this section I review studies that have applied these methods to test the etiology of both individual differences in ADHD symptoms and the diagnosis of ADHD.

#### *Family studies*

Previous studies demonstrate clearly that ADHD is familial. In comparison to the families of children without ADHD, the rate of ADHD is significantly higher in the biological relatives of probands with *DSM-III* ADD (e.g., Barkley, DuPaul, & McMurray, 1990), *DSM-III-R* ADHD (e.g., Biederman, Faraone, Keenan, Knee, & Tsuang, 1990), and *DSM-IV* ADHD (e.g., Faraone, Biederman, & Friedman, 2000; Friedman, Chhabildas, Budhiraja, Pennington, & Willcutt, in press). Specifically, 30-35% of the full siblings of ADHD probands also meet criteria for ADHD, indicating that the relative risk for ADHD is 6-8 times higher among first degree relatives of probands with ADHD than the base rate of ADHD in the population. Moreover, the relative risk is similar for relatives of both boys and girls with ADHD (Faraone et al., 2000), as well as the families of both Caucasian and African American probands (Samuel et al., 1999), indicating that the familiarity of ADHD is replicable across demographic groups.

The significant familiarity of ADHD is necessary support for the hypothesis that ADHD may be partially attributable to genetic influences, but does not provide sufficient evidence by itself. Because members of intact nuclear families share both genetic and family environmental influences, adoption and twin studies are necessary to disentangle the relative contributions of genes and environment.

#### *Adoption studies*

The biological relatives of an individual who is adopted at birth are related genetically to the individual but do not experience the same environmental influences (other than factors that influence mother and child during pregnancy). In contrast, adoptive relatives live in the same family environment but are biologically unrelated to the proband. Therefore, the relative influence of genes and family environment can be estimated by comparing the prevalence of a disorder among adoptive and biological relatives of individuals with the disorder. If a disorder is due to genetic factors the biological relatives of individuals with the disorder should exhibit a higher rate of the disorder than the population base rate,

whereas an elevated rate of the disorder among adoptive relatives would suggest that family environmental influences play a role in the etiology of the disorder.

The adoption study design is elegant and has been productive for some disorders (e.g., Cadoret, Leve, & Devor, 1997), but two specific constraints have limited the utility of adoption studies. First, adoptive parents may not be representative of the overall population of parents due to the laudable desire of adoption agencies to place adopted children in an optimal environment with high-functioning parents with access to many available resources (e.g., Plomin et al., 2001). Second, and most important, in societies in which adoption records are closed it is typically quite difficult to obtain information regarding the biological relatives of individuals who are adopted.

Due at least in part to these constraints only a handful of adoption studies of ADHD have been conducted, and in each of these studies data was unavailable regarding the biological parents of the adoptees (Alberts-Corush, Firestone, & Goodman, 1986; Sprich, Biederman, Harding Crawford, Mundy, & Faraone, 2000; van der Valk, Verhulst, Neale, & Boomsma, 1998). Despite this limitation, however, these studies provided important preliminary information regarding the etiology of ADHD. Results showed that the biological siblings and parents of nonadopted children with ADHD exhibited significantly higher rates of ADHD and associated attention problems, whereas adoptive parents of probands with ADHD were not significantly different from parents of comparison children without ADHD. These findings provide further evidence that ADHD is significantly familial, and suggest that the familial risk may be due to genetic rather than shared environmental factors.

### *Twin Studies*

By comparing the similarity of monozygotic (MZ) twins, who share all of their genes, to dizygotic (DZ) twins, who share half of their segregating genes on average, twin analyses provide direct estimates of the extent to which a trait is due to the influence of genes, shared environmental factors, and nonshared environmental factors (e.g., Plomin et al., 2001). The most straightforward analysis of twin data involves a comparison of the rate of concordance for the disorder of interest in pairs of MZ versus DZ twins. All twin studies of ADHD that reported concordance rates found that the rate of concordance was significantly higher among MZ pairs (58% - 82%) than same-sex DZ pairs (31% - 38%), providing further evidence that ADHD is significantly heritable (Levy, Hay, McStephen, Wood, & Waldman, 1997; Levy, McStephen, & Hay, 2001; Sherman, McGue, & Iacono, 1997; Willcutt, Pennington, & DeFries, 2000). In addition, the fact that the MZ concordance was less than 100% in all studies suggests that environmental influences also play a role in the etiology of ADHD.

Although the simplicity of a comparison of concordance rates is appealing, increasing evidence suggests that ADHD and most other psychological disorders are defined on the basis of a largely arbitrary diagnostic threshold on a quantitative measure (e.g., Barkley, 1998; Willcutt et al., 2000). Transformation of a continuous measure such as ADHD symptoms into a categorical variable (e.g., ADHD versus unaffected) results in the loss of important information pertaining to both severity within the disorder and

variability in subthreshold symptomatology. In contrast, alternative methods such as variance components analysis of unselected samples and multiple regression analysis of selected samples provide greater statistical power and versatility by using information about the entire continuum of scores. Therefore, we now turn to studies that have used these techniques to test the etiology of individual differences in ADHD symptoms and extreme ADHD scores.

*Individual differences.* Several large population-based twin studies have assessed the etiology of individual differences in ADHD symptoms. A total of over 10,000 twin pairs have participated in these studies to date. The studies used a variety of measures of ADHD, obtained ratings from parent and teachers, examined the etiology of individual differences in both males and females, and studied samples ascertained at locations in the United States (Eaves et al., 1997; Edelbrock, Rende, Plomin, & Thompson, 1995; Nadder, Silberg, Eaves, Maes, & Meyer, 1998; Neuman et al., 2001; Schmitz, Fulker, & Mrazek, 1995; Sherman, Iacono, & McGue, 1997; Willcutt, Shyu, Green & Pennington, 1995), the United Kingdom (Goodman & Stevenson, 1989; Kuntsi & Stevenson, 2001; Martin et al., 2002; Thapar, Hervas & McGuffin, 1995; Thapar, Harrington, & McGuffin, 2001), Australia (Levy et al., 1997; Waldman, Rhee, Levy, & Hay, 2001), and the Netherlands (Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2003).

In light of these diverse study designs, sampling procedures, and measures of ADHD, the results of these studies are strikingly consistent (Figure 1). All studies found that individual differences in ADHD symptoms are largely attributable to genetic influences, with an average heritability of .73 across all studies (Figure 1). The phenotypic variance in ADHD symptoms that is not accounted for by genetic influences is attributable to nonshared environmental influences (average  $e^2 = .27$ ), and estimates of shared environmental influences were not significant in any study. Some studies reported evidence of sibling contrast effects, such that DZ twins were rated as less similar than MZ twins based on knowledge about their zygosity rather than true differences in behavior (e.g., Eaves et al., 1997). However, parent ratings remained highly heritable even after contrast effects were included in the model (e.g., Eaves et al., 1997), and teacher ratings were significantly heritable even when the two twins were rated by different teachers. Thus, these results suggest that the high heritability of ADHD is not explained by contrast effects.

*Extreme scores.* Although studies of individual differences in ADHD symptoms are an important starting point, the diagnosis of ADHD is defined by a score at the extreme tail of the distribution. DeFries and Fulker (1985) described a multiple regression technique that provides a versatile and powerful test of the etiology of extreme scores on a continuous trait. Because a detailed description of this method is available elsewhere (e.g., DeFries & Fulker, 1985, 1988; Stevenson, 1992; Willcutt et al., 2003), I will summarize briefly the basic logic of the analysis and describe in more detail the results of studies which have used it to examine the etiology of extreme ADHD scores.

The DeFries and Fulker (DF) model is based on the regression of MZ and DZ cotwin scores toward the population mean when probands are selected due to extreme scores on a phenotype of interest (e.g.,

ADHD). Although scores of both MZ and DZ cotwins would be expected to regress toward the mean of the unselected population ( $\mu$ ), scores of DZ cotwins should regress further than scores of MZ cotwins to the extent that extreme scores are influenced by genes (Figure 2). After appropriate transformation of the data, the magnitude of this differential regression by zygosity provides a direct estimate of the heritability of the extreme ADHD scores of the proband group ( $h^2_g$ ).

To illustrate the DF method, a multiple regression model was fitted to DSM-IV ADHD symptom counts for twin pairs from the Colorado Learning Disabilities Research Center twin study, an ongoing study of the etiology of reading disability and ADHD at the University of Colorado (DeFries et al., 1997). For each of the three multiple regression analyses, all twins who exceeded the diagnostic threshold on the relevant measure of ADHD (i.e., inattention symptoms, hyperactivity-impulsivity symptoms, or the overall ADHD composite) were selected as probands. As shown in Table 1, MZ and DZ probands exhibited a similar number of symptoms for all three measures of ADHD, suggesting that the severity of the proband deficit was similar across zygosity. On each measure of ADHD, the mean score of the MZ cotwins regressed less toward the population mean than the mean score of the DZ cotwins, consistent with what would be expected if extreme ADHD scores are due to genetic influences. Indeed, when the multiple regression model was fitted the resulting estimates of group heritability were highly significant for all three measures of ADHD ( $h^2_g = .76 = .90$ ).

This high heritability is consistent with previous results from our sample (Gillis, Gilger, Pennington, & DeFries, 1992; Willcutt et al., 2000, 2001, 2003) and other studies (Gjone, Stevenson, & Sundet, 1996; Levy et al., 1997; Stevenson, 1992), providing additional converging evidence that ADHD is influenced strongly by genes. Moreover, the heritability estimates for extreme scores are similar to the estimates obtained for individual differences in ADHD symptoms, suggesting that similar genetic influences may contribute to both extreme ADHD scores and individual differences across the entire distribution of symptoms in the population (Gjone et al., 1996; Levy et al., 1997).

#### *Summary of behavioral genetic studies*

Behavior genetic studies indicate that ADHD is significantly familial, and that this familiarity is primarily due to genetic influences. In addition, nonshared environmental factors specific to the individual account for significant variance in ADHD. In contrast, estimates of the influence of shared environment were not significant in any adoption or twin studies, providing evidence against hypotheses that suggest that ADHD is attributable to factors that influence both twins similarly, such as ineffective parenting (e.g., Willis & Lovaas, 1977) or food additives (e.g., Feingold, 1975). Based on these results, subsequent studies have attempted to identify the specific environmental or genetic factors that increase the likelihood that a child will develop ADHD.

### Environmental influences associated with ADHD

Several studies of clinic-referred samples suggest that prenatal or perinatal complications have a small but significant association with ADHD (e.g., Breslau et al., 1996; Milberger, Biederman, Faraone, Guite, & Tsuang, 1997). Specific complications include low birth weight (e.g., Breslau et al., 1996), fetal distress (Hartsough & Lambert, 1985), and family problems during pregnancy (Milberger et al., 1997). These reported pre/perinatal factors may act in an additive or interactive manner with genetic influences to increase risk for ADHD, or may even represent an alternative etiological (i.e., non-genetic) pathway that is sufficient to cause the later development of ADHD in a subset of cases (Swanson, Oosterlaan, et al., 2000).

Children with ADHD or significant attention problems are also significantly more likely than comparison children to have been exposed prenatally to alcohol (e.g., Mick, Biederman, Faraone, Sayer, & Kleinman, 2002) or tobacco (Milberger et al., 1996, 1997). Importantly, these studies demonstrated that cigarette smoking and alcohol use during pregnancy significantly predicted the later development of ADHD even when parental ADHD was controlled, indicating that this relation is not confounded with the familiarity of ADHD. Most other studies or prenatal risk factors did not control for parental ADHD, however, suggesting that future research incorporating both genetic and environmental measures will be useful to specify further the nature of the relation between prenatal and perinatal risk factors and the later development of ADHD.

### Molecular Genetic Studies of ADHD

Although an estimated 99.9% of the deoxyribonucleic acid (DNA) sequence that comprises the human genetic code is identical among all people, the genetic sequence varies at tens of thousands of locations across the remaining 0.1% of the human genome. Many of these sequence differences, or polymorphisms, cause individual differences in protein production, which may then lead to individual differences in neural development or adult brain functioning if the polymorphism is in a gene that is expressed in the central nervous system. Previous studies have used two main methods to attempt to localize genes that increase susceptibility to ADHD. In this section I briefly describe these methods and review studies that have applied these techniques to ADHD.

#### *Methods to localize genes for a complex disorder*

*Candidate genes.* The candidate gene approach investigates the role of a specific gene identified because it is part of a biological system that is associated with the disorder. For example, because psychostimulant medication increases dopamine availability by blocking reuptake at the synapse (e.g., Amara & Kuhar, 1993), many studies have examined polymorphisms in genes that influence the dopamine pathway. By comparing the frequency of the different alleles at the candidate locus among individuals with and without ADHD, it is possible to test if any of the alleles are associated with increased risk for ADHD.

*Linkage analysis.* Although the candidate gene approach is useful when viable candidates can be identified, the pathophysiology of ADHD is not understood sufficiently to identify all plausible candidate genes. Therefore, family-based linkage analysis can be used to screen broad sections of the genome to identify regions which may contain additional genes that increase susceptibility to ADHD (e.g., Fisher et al., 2002). Because space constraints preclude a full description of this process, I summarize briefly the mechanisms of linkage, and refer the interested reader to more comprehensive explanations elsewhere (e.g., Faraone, Tsuang, & Tsuang, 1999; Pennington, 2002; Plomin et al., 2001).

All cells in the human body with the exception of gamete (sperm and egg) cells contain two full sets of the 23 human chromosomes. Gamete cells contain only one of each chromosome so that after fertilization the egg will have the full complement of 46 chromosomes (23 different chromosomes, with one copy of each inherited from the mother and one from the father). During meiosis parental cells divide to create gamete cells with a single set of the 23 chromosomes. Prior to dividing homologous chromosomes line up next to each other and one chromosome from each pair is included in each new gamete cell. However, a child sometimes does not inherit an ancestral chromosome in its entirety. Instead, when homologous chromosomes line up during meiosis they often physically cross over one another, and in the process may break and rejoin with the other chromosome. As a result of this *recombination*, the offspring will inherit a combination of segments from the two initial parental chromosomes.

Linkage analysis is based on the extent to which a disorder co-occurs with a specific allele at a marker locus whose location in the genome is known. If the marker locus and the gene that increases susceptibility to the disorder are close together on the same chromosome, recombination is unlikely to occur between the two loci and their alleles are likely to be transmitted together from parent to child. In contrast, if the marker and the susceptibility locus are on different chromosomes or are far apart on the same chromosome, recombination will frequently separate the marker allele from the risk allele at the susceptibility locus, and alleles at the two loci will be transmitted independently. Thus, linkage is indicated if the marker allele and disorder co-occur in members of a family significantly more frequently than would be expected by chance.

### *Candidate gene studies of ADHD*

Published studies have tested for an association between ADHD and 27 different candidate genes, and a series of studies by one group has examined over 20 additional candidate genes in a sample of individuals with ADHD and Tourette Syndrome (e.g., Comings et al., 2000). These studies have focused primarily on genes that influence dopamine, norepinephrine, and serotonin due to evidence that these neurotransmitters may play a role in the pathophysiology of ADHD or other psychopathology. For 14 of the 27 candidate genes a significant association with ADHD has been reported in at least one study; however, virtually all of these results have been replicated inconsistently or await independent replication (Table 2). Moreover, each of these genes appears to account for a relatively small proportion

of the variance in ADHD symptoms (e.g., Faraone, Doyle, Mick, & Biederman, 2001), suggesting that none are likely to be necessary or sufficient to cause ADHD.

Table 2 summarizes the results of all candidate gene studies published by the end of 2002. Because a detailed description of each of these candidate genes is beyond the scope of this review, I focus in more detail on studies of the dopamine transporter gene (DAT1) and the dopamine D4 receptor gene (DRD4), the candidate genes that have been investigated most frequently in relation to ADHD.

*DAT1.* The dopamine transporter functions to terminate the action of dopamine in the synapse by facilitating its re-uptake into the presynaptic membrane. The therapeutic efficacy of methylphenidate in the treatment of ADHD has been ascribed to blockade of the dopamine transporter, increasing the availability of dopamine in the synapse (e.g., Volkow et al., 1998). The DAT1 gene on chromosome 5 contains a 40 base-pair DNA sequence that repeats between 3 and 11 times in different people (Vandenbergh et al., 1992). Cook et al. (1995) first reported a significant association between ADHD and the 10-repeat allele of this polymorphism, and this result has since been replicated in several other independent samples (Table 2). However, an equal number of studies have failed to replicate this result, including one study that found a significant association in a sample ascertained in the United Kingdom but not in a sample recruited in Turkey (Curran, Mill, Tahir, et al., 2001).

Three additional factors complicate interpretation of results of studies of DAT1 and ADHD. First, the functional significance of this DAT1 polymorphism remains unclear (e.g., Barr, Xu, et al., 2001). Second, two recent medication studies of individuals with ADHD found that individuals with two copies of the 10 repeat allele exhibited poorer response to psychostimulant medication than individuals with one or zero copies of the allele (Roman, Szobot, et al., 2002; Winsberg & Comings, 1999), a somewhat counterintuitive result that underscores the complexity of the relation between specific genotypes and brain processes. Finally, population-based studies of allele frequencies have shown that approximately 75% of individuals in the general population have at least one copy of the putative risk allele at this polymorphism (e.g., Doucette-Stamm, Blakely, Tian, Mockus, & Mao, 1995), indicating clearly that this polymorphism is not sufficient to independently cause the development of ADHD. Instead, this polymorphism may combine with other genetic and environmental influences to confer liability sufficient to push an individual over the diagnostic threshold for ADHD, or may be associated with a polymorphism elsewhere in DAT1 that has functional significance for ADHD (Waldman et al., 1998).

*DRD4.* The DRD4 dopamine receptor gene on chromosome 11 contains a 48 base-pair DNA sequence that repeats between 3 and 9 times in human populations (Van Tol et al., 1992). LaHoste et al. (1996) first reported an association between ADHD and the 7-repeat allele of this polymorphism, and several subsequent studies have replicated this finding (Table 2). Similar to the results for DAT1, however, this result was not replicated in all samples and does not appear to be necessary or sufficient to cause ADHD. Moreover, the association with ADHD is much stronger in case-control comparisons than in family-based designs, suggesting that some significant results may be due to differences in gene

frequencies in the populations from which the ADHD and comparison samples were drawn (Faraone et al., 2001).

### *Linkage studies of ADHD*

The candidate gene studies described previously provide important data regarding the relation between ADHD and numerous candidate genes that influence neurotransmission. The inconsistent results across studies and the small effect size for each of these candidate genes suggest that the known candidate genes are not sufficient to explain fully the genetic etiology of ADHD. Therefore, a recent study conducted a genome-wide screen to identify chromosomal regions that may contain other genes that increase susceptibility to ADHD (Fisher et al., 2002; Smalley et al., 2002), and another tested for linkage of ADHD to DNA markers in a targeted region on chromosome 6 (Willcutt et al., 2002, 2003).

As described previously, a genome screen is used to systematically test the entire genome for chromosomal regions that may contain genes that increase susceptibility to a disorder. This method also facilitates the exclusion of regions which are statistically unlikely to contain a gene for the disorder. The screen conducted by Fisher et al. (2002) found no evidence anywhere in the genome for a gene with a large effect on ADHD (relative risk  $\geq 3$ ), although they identified regions that may contain genes with smaller effects on chromosomes 5, 10, 12, and 16. In contrast, their results enabled them to exclude statistically a gene of large effect from over 95% of the genome. Of the candidate genes that were identified in previous association studies, only the serotonin transporter gene and dopamine D5 receptor genes are in regions of significant positive linkage. Many of the remaining candidate genes, including DRD4 and DAT1, map to chromosomal regions that could be excluded statistically in the genome screen.

In our study (Willcutt et al., 2002, 2003) we targeted a specific region on chromosome 6p because it contains a well-replicated quantitative trait locus (QTL) for reading disability (e.g., Cardon et al., 1994; Fisher et al., 1999; Gayán et al., 1999), a disorder that frequently co-occurs with ADHD (e.g., Willcutt & Pennington, 2000). A QTL is a gene that increases susceptibility to a disorder, but is neither a necessary nor sufficient cause by itself. Our results revealed significant linkage of ADHD to several DNA markers in this region, suggesting that a QTL in this region is also a susceptibility locus for ADHD. Moreover, bivariate analyses revealed significant bivariate linkage for ADHD and four measures of reading difficulty, suggesting that comorbidity between RD and ADHD is due at least in part to this QTL.

### *Summary of molecular genetic studies of ADHD*

In summary, although the limited number of studies and inconsistency of results across samples preclude definitive conclusions at the present time, these studies clearly suggest that multiple genes are involved in the etiology of ADHD, and that few if any of these genes are necessary or sufficient to cause ADHD. The variability of results across studies is not unique to ADHD; a similar pattern is apparent in genetic studies of other complex psychiatric phenotypes such as schizophrenia (e.g., Riley & McGuffin, 2000), addictive behaviors (e.g., Crabbe, 2002), and bipolar disorder (e.g., Craddock & Jones, 2001). In

light of the complexity of these results, it is not surprising that ADHD is a heterogeneous disorder that may include meaningful diagnostic subtypes. In the final section of the chapter, I discuss future directions for behavioral and molecular genetic studies of ADHD, including adaptations of these methods to test the validity of putative diagnostic subtypes.

#### Future directions

In this final section I describe ways that the behavioral and molecular genetic techniques described in the previous sections have been extended to test specific research questions regarding the diagnostic nosology and neuroscience of ADHD. The first section discusses ways that etiologically informative methods can be employed to improve diagnostic nosology, using studies of *DSM-IV* ADHD as an example. The second section describes the identification and utilization of pathophysiological endophenotypes to facilitate a better understanding of the specific functional impact of genetic and environmental risk factors, and the final section describes possible ways that results of molecular genetic studies may be used to improve treatment efficacy.

#### *The validity of the DSM-IV ADHD subtypes*

When considered in isolation, information about the etiology of a trait provides no information regarding the diagnostic validity of the behavior. For example, although individual differences in physical stature are almost entirely attributable to genetic influences (e.g., Plomin, DeFries, & McClearn, 1990), no one would suggest that a new disorder should be defined based solely on extreme height. However, when a cluster of symptoms has first been shown to be internally consistent and associated with clear functional and neuropsychological impairment, etiologically informative methods can be used to conduct powerful tests of the validity of putative diagnostic subtypes. If the *DSM-IV* ADHD subtypes are in fact different manifestations of the same overarching disorder, the three subtypes should be attributable to at least some of the same etiological influences. In contrast, if the subtype taxonomy has discriminant validity it should also be possible to identify etiological influences that are specific to each subtype.

*Family studies.* Several family studies have tested whether the *DSM-IV* ADHD subtypes “breed true”, such that biological family members of probands with one of the subtypes are at increased risk for that specific subtype and not the other subtypes (Faraone et al., 2000; Levy et al., 2001; Smalley et al., 2000; Todd et al., 2001). All four studies found that biological relatives of probands with any *DSM-IV* ADHD subtype are at increased risk for ADHD. However, although one study reported evidence of subtype-specific familiarity (Levy et al., 2001), the other studies found that familial risk factors for the inattentive and combined subtypes were general and not specific to either subtype. In contrast, family members of probands with the hyperactive-impulsive type exhibited specific elevations of the hyperactive-impulsive subtype in all samples, although the number of probands in each study was relatively small.

Therefore, existing family data provide only weak evidence of discriminant validity between the *DSM-IV* inattentive and combined subtypes, and larger samples will be necessary to test more conclusively whether the hyperactive-impulsive type is familial.

*Twin studies.* Results of twin studies indicate that individual differences in levels of hyperactivity-impulsivity and inattention symptoms are highly heritable (e.g., Hay, McStephen, & Levy, 2001; Sherman, Iacono, & McGue, 1997; Willcutt et al., 1995; 2000), and that longitudinal stability of these symptoms between early and late childhood is explained primarily by heritable influences (Hay et al., 2001).

As a preliminary test of the etiology of the *DSM-IV* ADHD subtypes, we used an extension of the DF multiple regression model described previously to test if the etiology of inattention and hyperactivity-impulsivity symptoms varied as a function of the proband's score on the other symptom dimension (Willcutt et al., 2000; 2001; 2003). Our results revealed that extreme inattention scores were highly heritable whether the proband met criteria for the *DSM-IV* inattentive or combined type ( $h^2_g = .88 - .92$ ). In contrast, whereas extreme hyperactivity-impulsivity scores were also highly heritable when the proband met criteria for the *DSM-IV* combined type ( $h^2_g = .92$ ), the heritability of hyperactivity-impulsivity symptoms was substantially lower ( $h^2_g = .06 - .16$ ) and nonsignificant when the proband met criteria for the hyperactive-impulsive type. Similarly, Todd et al. (2001) reported high heritability for *DSM-IV* combined type (MZ concordance = 63%, DZ concordance = 13%) and inattentive type (MZ concordance = 60%, DZ concordance = 16%) in a sample of female twins with ADHD, whereas the hyperactive-impulsive type was substantially less heritable (MZ concordance = 20%, DZ concordance = 11%). These low heritability estimates suggest that the etiology of the hyperactive-impulsive type may be different from the etiology of the combined and inattentive types. However, in contrast to these results, Levy et al. (2001) found that the hyperactive-impulsive type was more strongly heritable in the Australian Twin ADHD Project, suggesting again that additional research is needed to answer this question definitively.

*Molecular genetic studies.* A series of studies by one group provide an excellent example of the use of molecular genetic techniques to test the validity of diagnostic subtypes (Rowe et al., 1998; Waldman et al., 1998). Their results revealed that the 10-copy allele of the DAT1 polymorphism was associated more strongly with the *DSM-IV* combined type than the inattentive type (Waldman et al., 1998). In contrast, the 7-repeat DRD4 allele was associated more strongly with the inattentive type than the combined type in case-control comparisons (Rowe et al., 1998), although neither result was significant in family-based analyses. These results provide the strongest evidence to date for the discriminant validity of the inattentive and combined types, although they should be interpreted with caution until they can be replicated in an independent sample. However, whether or not these findings replicate in later studies, they illustrate clearly how molecular genetic methods will help to clarify the diagnostic nosology of ADHD and other psychiatric disorders in the future.

### *Endophenotypes*

Another promising future direction for molecular genetic studies of complex disorders is the identification of endophenotypes, continuous measures of pathophysiological processes that may mediate or moderate the relation between gene action and the final phenotypic manifestation of the disorder (e.g., Cannon, Gasperoni, van Erp, & Rosso, 2001; Gottesman, McGuffin, & Farmer, 1987). Because the multiple genes that are involved in the etiology of ADHD are likely to impact different aspects of neural systems, it may be easier to detect the effect of a particular gene on measures of these more specific phenotypes. For example, studies of reading disability obtained stronger evidence of linkage for measures of several specific reading-related language processes than for an overall reading composite measure (Fisher & DeFries, 2002). Similarly, research on candidate genes associated with schizophrenia demonstrated an association between the  $\alpha 7$ -nicotinic cholinergic receptor gene and a specific phenotype characterized by failure to habituate to repeated auditory stimuli in an evoked response potential paradigm (e.g., Freedman et al., 2000).

As a first step toward the identification of optimal endophenotypes for linkage or candidate gene studies of ADHD, twin analyses can be used to test the etiology of bivariate relations between ADHD and specific neurocognitive deficits. Significant bivariate heritability would indicate that a neurocognitive deficit is attributable at least in part to the same genes as ADHD, and the strength of bivariate heritability can be compared across measures to evaluate the potential utility of each measure as an endophenotype. Results from two recent twin studies illustrate this approach (Chhabildas, Pennington, & Willcutt, 2003; Kuntsi & Stevenson, 2001).

Kuntsi and Stevenson (2001) administered a battery of neuropsychological tasks to twins with and without ADHD, and found that elevations of ADHD symptoms were attributable to the same genes that influence variability of reaction time, an index of arousal regulation. Similarly, due to results suggesting that ADHD is associated with deficits on a variety of measures of executive functions (EF; e.g., Barkley, 1997; Chhabildas, Pennington, & Willcutt, 2001; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002), we examined the etiology of the relation between ADHD and EF in the CLDRC sample (Chhabildas et al., 2003). Estimates of bivariate heritability were significant for measures of response inhibition, verbal working memory, and processing speed, suggesting that these markers may be useful endophenotypes for future molecular genetic studies.

Molecular genetic studies have also begun to test for relations between neurocognitive endophenotypes and the candidate genes discussed in the previous section. For example, one recent study found that infants with the 7-repeat DRD4 allele exhibited deficits in sustained attention during a structured play situation and information-processing task (Auerbach, Benjamin, Faroy, Geller, & Ebstein, 2001). In contrast, two recent studies found that neuropsychological deficits were only apparent in the group of children with ADHD who did *not* have the 7-repeat allele (Manor et al., 2002; Swanson, Oosterlaan, et al., 2000), and one study reported no association between DRD4 alleles and brain morphometric variables (Castellanos et al., 1998). These results again demonstrate the complex results that are likely to be obtained in studies of the relation between candidate genes and endophenotypes,

particularly in small samples. By applying these techniques in larger, well-characterized samples, future studies of endophenotypes will help to clarify the effect of each candidate gene, and will provide an important tool to facilitate the dissection of the overall pathophysiology of ADHD into specific component processes (e.g., Fisher & DeFries, 2002).

### *Treatment implications*

Finally, results of future behavioral and molecular genetic studies are likely to facilitate the development and application of primary prevention and early intervention techniques that would be impossible without understanding of the etiology of ADHD. For example, if a perinatal screening revealed significant genetic susceptibility to ADHD, parents could be provided with education and consultation regarding child behavior management techniques that may help to minimize or eliminate the impairment caused by symptoms of ADHD if their infant were to develop such symptoms. Similarly, by providing a better understanding of underlying pathophysiology, molecular genetic techniques will inform the development of tertiary pharmacological or psychosocial treatments that directly target the specific neurophysiological mechanisms that are compromised in ADHD.

### Conclusions

In summary, available data suggest that ADHD and virtually all other psychological traits and disorders are caused by the combination of many genetic and environmental risk factors, none of which is necessary or sufficient to cause the development of ADHD by itself. Moreover, it is likely that interactions among these risk factors may contribute to susceptibility to ADHD, and other variables may moderate the relation between risk factors and phenotypic manifestation. Therefore, to fully understand the complex etiology of ADHD future studies will need to type each of these genes and measure each environmental risk factor in a single well-characterized sample of individuals with ADHD. Multivariate analyses of these data could then be conducted to examine the relative contribution of each genetic or environmental factor to the development of ADHD, and to test whether each of these influences acts independently of the others or interacts with other influences to confer liability to ADHD.

In closing, it is worth noting that procedures for DNA collection and genetic analysis continue to become more automated and efficient. Through collaboration with experts in DNA analysis, it is rapidly becoming possible for psychological researchers with relatively modest budgets and little previous training to incorporate genetically informative methods as one part of their study. The capability to apply these methods more broadly will facilitate an extraordinary kind of collaborative synergy between behavior genetic researchers and investigators focusing on the neurocognitive aspects of ADHD, and can only serve to strengthen studies in both domains.

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Table 1

*Mean number of ADHD symptoms of monozygotic and dizygotic probands selected for DSM-IV ADHD and their cotwins*

Symptom dimension	Monozygotic Pairs		Dizygotic Pairs		$h^2_g$ (SE)	t
	Proband M (SD)	Cotwin M (SD)	Proband M (SD)	Cotwin M (SD)		
DSM-IV Inattention	8.00 (1.02)	6.33 (3.12)	7.98 (1.09)	3.03 (3.42)	0.90 (.18)	4.86***
DSM-IV Hyper-impuls	7.17 (1.39)	5.03 (3.19)	6.58 (1.73)	2.36 (2.58)	0.76 (.22)	3.52***
Total DSM-IV ADHD	12.26 (3.31)	10.43 (5.65)	11.97 (3.17)	5.53 (5.38)	0.84 (.19)	4.25***

*Note.* Number of twin pairs = 60 MZ, 65 DZ for inattention; 40 MZ, 45 DZ for hyperactivity-impulsivity; 70 MZ, 65 DZ for total ADHD

\*\*\* =  $p < .001$

Table 2

*Candidate gene studies of ADHD*

Candidate Gene	Studies reporting a significant relation	Studies reporting no significant relation	Percent of Studies Reporting a Significant Effect
<i>Dopamine system genes</i>			
Dopamine transporter	9, 12, 14 <sup>a</sup> , 16, 20, 53, 68	14 <sup>a</sup> , 26, 44, 47, 51, 60, 65	50%
D1 receptor		32	0%
D2 receptor		32, 55, 66	0%
D3 receptor		7, 45, 48	0%
D4 receptor case-control analysis	13, 26, 34, 43, 46, 51, 53, 54, 61	11, 41	82%
D4 receptor family-based analysis	4, 19, 25, 39 <sup>b</sup> , 58, 59, 61, 63	2 <sup>b</sup> , 18, 23, 26, 33, 38 <sup>c</sup> , 39, 43, 46, 54, 67	42%
D5 receptor	16	5, 48, 63	25%
Dopamine Beta-hydroxylase	16, 52	48, 69 <sup>d</sup>	50%
DOPA decarboxylase	32	22	50%
Tyrosine hydroxylase		32, 48	0%
<i>Serotonin system genes</i>			
Serotonin transporter	29, 37, 50, 56		100%
Serotonin Receptor 1b	21		100%
Serotonin Receptor 2a	35 <sup>e</sup>	21 <sup>f</sup>	50%
Serotonin Receptor 2b	49		100%
Tryptophan hydroxylase		64	0%
<i>Adrenergic receptor genes</i>			

$\alpha 1c$		8	0%
$\alpha 2a$		70	0%
$\alpha 2c$		8	0%
<i>Monoamine oxidase genes</i>			
A	27	48	50%
B		28	0%
<i>Nicotinic receptor genes</i>			
acetylcholine $\alpha 4$ subunit gene		31	0%
acetylcholine $\alpha 7$ subunit gene		30	0%
<i>Other candidate genes</i>			
Catechol-O-methyltransferase	17	6, 24, 32, 48, 62	17%
DXS7	27	36	50%
Interleukin-1 receptor	57		100%
Norepinephrine transporter		3, 40	0%
Synaptosomal-associated protein 25	10, 42	1 <sup>d</sup>	67%

*Note.* Studies included in the table: 1. Barr, Feng, et al., 2000; 2. Barr, Feng, et al., 2001; 3. Barr et al., 2002; 4. Barr, Wigg, Bloom, et al., 2000; 5. Barr, Wigg, Feng, et al., 2000; 6. Barr, Wigg, Malone et al., 2000; 7. Barr, Wigg, Wu et al., 2000; 8. Barr, Wigg et al., 2001; 9. Barr, Xu, et al., 2001; 10. Brophy et al., 2002; 11. Castellanos et al., 1998; 12. Cook et al., 1995; 13. Curran, Mill, Sham et al., 2001; 14. Curran, Mill, Tahir et al., 2001; 15. Daly et al., 1998; 16. Daly et al., 1999; 17. Eisenberg et al., 1999; 18. Eisenberg et al., 2000; 19. Faraone et al., 1999; 20. Gill et al., 1997; 21. Hawi et al., 2002; 22. Hawi et al., 2001; 23. Hawi, McCarron, et al., 2000; 24. Hawi, Millar et al., 2000; 25. Holmes et al., 2002; 26. Holmes et al., 2000; 27. Jiang et al., 2000; 28. Jiang et al., 2001; 29. Kent et al., 2002; 30. Kent, Green, et al., 2001; 31. Kent, Middle et al., 2001; 32. Kirley et al., 2002; 33. Kotler et al., 2000; 34. LaHoste et al., 1996; 35. Levitan et al., 2002; 36. Lowe et al., 2001; 37. Manor et al., 2001; 38. Manor et al., 2002; 39. McCracken et al., 2000; 40. McEvoy et al., 2002; 41. Mill, Caspi et al., 2002; 42. Mill, Curran, et al., 2002; 43. Mill et al., 2001; 44. Muglia, Jain, Inkster, & Kennedy, 2002; 45. Muglia, Jain, & Kennedy, 2002; 46. Muglia et al., 2000; 47. Palmer et al., 1999; 48. Payton et al., 2001; 49. Quist et al., 2000; 50.

Retz et al., 2002; 51. Roman et al., 2001; 52. Roman et al., 2002; 53. Rowe et al., 2001; 54. Rowe et al., 1998; 55. Rowe et al., 1999; 56. Seeger et al., 2001; 57. Segman et al., 2002; 58. Smalley et al., 1998; 59. Sunohara et al., 2000; 60. Swanson, Flodman, et al., 2000; 61. Swanson et al., 1998; 62. Tahir, Curran et al., 2000; 63. Tahir, Yazgan, et al., 2000; 64. Tang et al., 2001; 65. Todd, Jong et al., 2001; 66. Todd & Lobos, 2002; 67. Todd, Neuman et al., 2001; 68. Waldman et al., 1998; 69. Wigg et al., 2002; 70. Xu et al., 2001.

<sup>a</sup>Association significant in UK sample, nonsignificant in Turkish sample. <sup>b</sup>Tested a different polymorphism of the DRD4 gene than the other studies of ADHD. <sup>c</sup>Significant family-based association with the short allele, in contrast to other positive results suggesting the long allele as the risk allele. <sup>d</sup> $p < .10$ . <sup>e</sup>women with seasonal affective disorder. <sup>f</sup>Although this relation was not significant in the total sample, it was significant in the Irish sample alone.

Figure Captions

*Figure 1.* Results of population-based twin studies of the etiology of individual differences in ADHD symptoms. P = parent ratings, T = teacher ratings. \* indicates results were averaged across several measures due to similar results.

*Figure 2.* Expected co-twin means if extreme ADHD scores are due to genetic influences.



