

Candidate Gene Studies of Attention-Deficit/Hyperactivity Disorder

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A growing body of behavioral and molecular genetics literature has indicated that the development of attention-deficit/hyperactivity disorder (ADHD) may be attributed to both genetic and environmental factors. Family, twin, and adoption studies provide compelling evidence that genes play a strong role in mediating susceptibility to ADHD. Molecular genetic studies suggest that the genetic architecture of ADHD is complex, while the handful of genome-wide scans conducted thus far is not conclusive. In contrast, the many candidate gene studies of ADHD have produced substantial evidence implicating several genes in the etiology of the disorder. For the 8 genes for which the same variant has been studied in 3 or more case-control or family-based studies, 7 show statistically significant evidence of association with ADHD based on pooled odds ratios across studies: the dopamine D₄ receptor gene (*DRD4*), the dopamine D₅ receptor gene (*DRD5*), the dopamine transporter gene (*DAT*), the dopamine β-hydroxylase gene (*DBH*), the serotonin transporter gene (*5-HTT*), the serotonin receptor 1B gene (*HTR1B*), and the synaptosomal-associated protein 25 gene (*SNAP25*). Recent pharmacogenetic studies have correlated treatment nonresponse with particular gene markers, while preclinical studies have increased our understanding of gene expression paradigms and potential analogs for human trials. This literature review discusses the relevance and implications of genetic associations with ADHD for clinical practice and future research. (*J Clin Psychiatry* 2006;67[*suppl* 8]:13–20)

Attention-deficit/hyperactivity disorder (ADHD) is a complex neurobehavioral condition characterized by inattention, hyperactivity, and impulsivity. Although ADHD presents clinically with a high degree of heterogeneity, and molecular genetics studies further the understanding of this disorder, the pathogenesis of ADHD remains elusive.¹ Data from family, twin, and adoption studies show that genes play a substantial role in the etiology of ADHD.^{1,2} Therefore, investigation into the biological underpinnings of the pathogenesis of ADHD have focused on candidate genes identified in neurobiological studies. Association studies, such as case-control and family-based designs, have sought to determine to what degree gene products, such as neurotransmitters, are rel-

evant to the etiology of ADHD. Case-control study designs compare allele frequencies between patients with ADHD and control subjects who do not have ADHD. Alleles that confer risk for ADHD should be more common among patients with ADHD. Family-based designs, on the other hand, compare the alleles transmitted by parents to ADHD children with the alleles they do not transmit. If an allele increases the risk for ADHD, it should be more common among the transmitted alleles than the nontransmitted alleles.

The association between ADHD and the putative risk alleles can be quantified by deriving the odds ratio (OR) or relative risk (RR) statistic. While many studies (see review by Faraone et al.²) have explored the relationship between candidate genes and the pathophysiology of ADHD, only 8 genes with the same variant have indicated significant pooled ORs in 3 or more case-control or family-based studies (Table 1).^{2,3}

The catecholaminergic gene variants, particularly those related to dopamine, have been studied the most. While the catecholaminergic genes hold potential promise in furthering the understanding of associations with ADHD, the heterogeneity between the studies, as well as evidence from other candidate gene studies, further solidifies the presupposition of ADHD as a polygenic and highly heritable neurobehavioral condition.

This article is divided into 2 sections. The first summarizes the candidate gene studies computed by Faraone

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Table 1. Significant Pooled Odds Ratios (ORs) for Gene Variants Examined in 3 or More Case-Control or Family-Based Studies^a

Gene	Study Design	Pooled OR	95% CI
Dopamine D ₄ receptor (exon III VNTR, 7-repeat)	Family	1.16	1.03 to 1.31
Dopamine D ₄ receptor (exon III VNTR, 7-repeat)	Case control	1.45	1.27 to 1.65
Dopamine D ₅ receptor (CA repeat, 148 bp)	Family	1.24 ^b	1.12 to 1.38
Dopamine transporter (VNTR, 10-repeat)	Family	1.13	1.03 to 1.24
Dopamine β-hydroxylase (TaqI A)	Case control	1.33	1.11 to 1.59
<i>SNAP25</i> (T1065G)	Family	1.19	1.03 to 1.38
Serotonin transporter (5-HTTLPR long)	Case control	1.31	1.09 to 1.59
<i>HTR1B</i> (G861C)	Family	1.44	1.14 to 1.83

^aReprinted with permission from Faraone et al.² OR and CI values were computed by Faraone et al.²

^bData from Lowe et al.³

Abbreviations: bp = base pairs, CI = confidence interval, *HTR1B* = 5-hydroxytryptamine (serotonin) receptor 1B, *SNAP25* = synaptosomal-associated protein 25, VNTR = variable number of tandem repeats.

et al.² for gene variants that indicated an association with ADHD. The second summarizes pharmacogenetic findings that help to provide gene markers that predict medication efficacy and adverse events.

CATECHOLAMINERGIC GENES

Attention-deficit/hyperactivity disorder may disrupt optimal performance of the circuits connecting the cerebellum and striatal structures to the prefrontal cortex (PFC), resulting in the hallmark phenotypic symptoms of poor attention, impulsivity, and hyperactivity. Neuropsychological measurements of ADHD subjects reveal deficits in tasks requiring PFC function, an area that has a large number of connections to motor, sensory, and subcortical structures. Executive functions are also mediated by the circuitry of the PFC. Receptor agonists of interest for their role in the pathophysiology of ADHD include the dopamine D₄ receptor gene (*DRD4*), the dopamine D₅ receptor gene (*DRD5*), and the dopamine transporter gene (*DAT*).

Dopamine D₄ Receptor Gene (*DRD4*)

DRD4 is prevalent in the frontal-subcortical networks and has been implicated in the pathophysiology of ADHD.⁴ A meta-analysis by Faraone et al.⁵ reported that a polymorphism, the 7-repeat tandem allele on exon III, yielded a combined estimated OR of 1.9 (95% CI = 1.4 to 2.2) in case-control studies and a combined estimated OR of 1.4 (95% CI = 1.1 to 1.6) in family-based studies. Study designs indicated biases for neither significance nor magnitude of the OR results. Overall findings implicating *DRD4* in ADHD have been positive as well as divergent. However, despite divergent findings, when all studies of the exon III polymorphism were pooled and reported by Faraone et al.,² the association with ADHD remained statistically significant (OR = 1.45 [95% CI = 1.27 to 1.65] in case-control studies and OR = 1.16 [95% CI = 1.03

to 1.31] in family-based studies). Studies using symptom dimensions rather than categorical diagnoses suggest that *DRD4* may be particularly relevant to symptoms of inattention.^{6,7}

Dopamine D₅ Receptor Gene (*DRD5*)

Studies of *DRD5* polymorphisms have revealed variability in terms of associations with ADHD. Excess transmission of the 148-base pair (bp) allele in ADHD probands has been found strongest among families without parental history of ADHD,⁸ yet a study⁹ of 81 families from the United Kingdom showed no evidence for an association with the dinucleotide repeat polymorphism. In addition, a Canadian study¹⁰ found no significant association with the 148-bp allele but significant undertransmission of the 146-bp allele, which was also reported by an American group.¹¹ Another study¹² of 3 markers found an association only for a downstream dinucleotide repeat not assessed in other studies.

Despite the variability in these study results, a meta-analysis¹³ of family-based studies revealed a significant association between *DRD5* and ADHD that suggested that previous nonsignificant findings may have been due to inadequate statistical power. Subsequently, a more recent family-based analysis³ identified a significant association of the 148-bp allele with inattentive and combined subtypes of ADHD (OR = 1.2; 95% CI = 1.1 to 1.4). A significant association was also noted in a study¹⁴ that was not limited to inattentive and combined subtypes.

Dopamine D₂ Receptor Gene (*DRD2*)

DRD2 has been studied less extensively in ADHD than *DRD4* and *DRD5*. A case-control study¹⁵ of patients with ADHD (mostly comorbid with Tourette's disorder) found an association with the TaqI A1 allele of *DRD2*. Conversely, a family-based study¹⁶ found no association between *DRD2* and ADHD. This discordance may be the result of differences between family-based versus case-

control studies, but the study that indicated an association may have been influenced by the inclusion of patients with comorbid Tourette's disorder. On aggregate, studies to date suggest little or no association between *DRD2* and ADHD.

Dopamine D₃ Receptor Gene (*DRD3*)

DRD3 does not appear to be associated with ADHD. Combining all extant studies,² the pooled OR of 1.2 is not statistically significant.

Dopamine Transporter Gene (*DAT*, *SLC6A3*)

The *DAT* (*SLC6A3*) has been considered a suitable candidate for ADHD for several reasons. First, 1 mechanism of stimulant medications blocks the dopamine transporter as a means for achieving therapeutic effect.¹⁷ Second, eliminating the *DAT* function in mice^{18,19} elicits hyperactivity and deficits in inhibitory behavior, 2 hallmark characteristics of ADHD. Administering stimulants to "knockout" mice helps to ameliorate hyperactivity, which replicates the response in children treated with stimulants. Lastly, similar findings²⁰ in mice were noted when *DAT* activity was reduced to 10% of normal.

In a family-based association study, Cook et al.²¹ first reported an association between ADHD and the 10-repeat allele of the variable number of tandem repeats (VNTRs) located in the 3' untranslated region of *DAT*. A meta-analysis²² showed a small positive, but nonsignificant, OR of 1.16, which was suggestive of significant heterogeneity among data sets. A second meta-analysis¹³ utilized 11 family-based samples (9 of which were part of the first meta-analysis²²) but revealed a nonsignificant OR of 1.27. Subsequent to the publication of the 2 meta-analyses, several additional studies²³⁻²⁷ have appeared in the literature, many of them involving family-based twin samples, but with divergent results. Other studies²⁸⁻³⁰ have examined quantitative traits, rather than the presence or absence of ADHD, for association with *DAT* and reported findings ranging from an association with increases in symptom severity²⁹ to no association when ADHD was considered as a continuous trait.³⁰

Pooled results from family-based studies as reviewed by Faraone et al.² indicate a small but significant OR (OR = 1.13, 95% CI = 1.03 to 1.24), suggesting that the *DAT* merits further investigation but that its effect is modest.

Dopamine β-Hydroxylase Gene (*DBH*)

Dopamine β-hydroxylase (DBH) is the primary enzyme responsible for the conversion of dopamine to norepinephrine. A case-control study²⁶ and family-based studies^{8,31} have supported an association between *DBH* and ADHD. The logistic regression analysis used in the case-control study²⁶ indicated a significant association between the A1 allele of the TaqI polymorphism and ADHD

(OR = 1.96; 95% CI = 1.01 to 3.79). One family-based study⁸ examined the TaqI polymorphism in an Irish sample of 86 trios and 19 parent-child pairs and found a significant association (RR = 1.31) between the A2 allele and ADHD. The A2 allele strongly correlated with the presence of paternal history of ADHD, with the strongest association for the combined subtype. In a Brazilian family-based study³¹ of 88 families, an association with the A2 allele and ADHD, especially the combined subtype, was also found. However, this latter sample did not correlate excessive transmission of the A2 allele with parental history of ADHD.

Conversely, a few family studies^{9,32,33} have shown no evidence of linkage or association between *DBH* and ADHD. Wigg et al.³² reported no excess transmission of the A2 allele, no evidence of linkage or association for the dinucleotide repeat polymorphism and an insertion/deletion polymorphism in the 5' to transcription start site, and no correlation for haplotypes for the 3 polymorphisms. Payton et al.⁹ found no association between the G/T single-nucleotide polymorphism (SNP) in exon 5 of *DBH* and ADHD. Finally, Hawi et al.³³ found no evidence for association for the additional polymorphism analyses of the MspI polymorphism in intron 9 or the EcoNI restriction fragment length polymorphism (RFLP) in exon 2; however, preferential transmission of a 2-marker haplotype comprising allele 1 of the exon 2 polymorphism and A2 of the TaqI polymorphism was noted in ADHD cases.

Despite the mixed evidence for association between *DBH* and ADHD, when the family-based studies were pooled by Faraone et al.,² they jointly suggested a significant association between ADHD and the 5' TaqI polymorphism (OR = 1.33, 95% CI = 1.11 to 1.59).

Tyrosine Hydroxylase Gene (*TH*)

Tyrosine hydroxylase (TH) plays a key role in the synthesis of dopamine by catalyzing the conversion of tyrosine to dihydroxy-phenylalanine (DOPA). Thus far, only 3 studies^{9,34,35} have examined the association between polymorphisms in *TH* and ADHD, and all have been negative.

Catechol-O-methyltransferase Gene (*COMT*)

Catechol-O-methyltransferase (COMT) plays a major role in the catabolism of dopamine, norepinephrine, and epinephrine, and is thought to play a major role in the PFC. Its role in ADHD, however, remains unclear. Several family-based studies^{9,36-39} have revealed no significant association between the Val108Met polymorphism in the *COMT* gene, which yields either a high-active or low-active form of COMT, and ADHD. Conversely, 2 studies^{40,41} reported statistically significant associations. Although the authors of 1 study⁴⁰ subsequently corrected their report to include less overtransmission of the Val allele than was originally reported, pooled analysis² of these

studies showed no evidence of an association between ADHD and *COMT* (OR = 1.0, $p = \text{NS}$).

Monoamine Oxidase A Gene (*MAOA*)

The monoamine oxidase A (MAO-A) enzyme moderates levels of norepinephrine, dopamine, and serotonin in the central nervous system (CNS). The absence of or deficiencies in the MAO-A enzyme, as observed in knockout mice,⁴² resulted in numerous abnormalities in these neurotransmitter systems. A recent Irish family-based study⁴³ of 179 nuclear families examined 4 *MAOA* polymorphisms: the 30-bp promoter VNTR, a 6-repeat CA microsatellite in intron 2, the 941 G/T SNP in exon 8, and the A/G SNP in intron 12. A transmission disequilibrium test revealed a significant association of the 941 G allele (OR = 1.7, $p = .03$), while haplotype analyses⁴³ revealed increased transmission of the 30-bp promoter VNTR, the 6-repeat allele of the CA microsatellite, and the G allele of the 941 G/T SNP ($p = .01$) to ADHD cases. The promoter region VNTR was also associated with ADHD in an X-linked case-control study⁴⁴ of 110 Israeli males and 19 Israeli females with ADHD versus controls. A large effect was noted in the small subset of females with ADHD, and an association was noted between the risk polymorphism and errors of commission on a neuropsychological test of attention. An association between a dinucleotide VNTR and ADHD was found in a sample of 82 Chinese families,⁴⁵ while these findings were not replicated in a Caucasian cohort.⁹ Mixed results and results that could not be replicated among different ethnic cohorts indicate no association between *MAOA* and ADHD.

THE NORADRENERGIC SYSTEM

Noradrenergic Receptor Genes *ADRA2A*, *ADRA2C*, and *ADRA1C*

Much like dopamine, norepinephrine is an important catecholamine that is known to have a substantial role in mediating cognition. Reduction in ADHD symptoms has been observed in trials utilizing pharmacotherapies that directly increase endogenous norepinephrine and dopamine (i.e., the stimulants methylphenidate, dextroamphetamine, and amphetamine; and the noradrenergic nonstimulant atomoxetine).⁴⁶ However, the 3 adrenergic receptors that have been examined in ADHD, the α_{2A} -adrenergic receptor (*ADRA2A*),⁴⁷⁻⁵⁰ the α_{2C} -adrenergic receptor (*ADRA2C*),⁵¹⁻⁵³ and the α_{1C} receptor (*ADRA1C*),⁵¹ have shown no association with ADHD. Because studies to date have been limited by small sample sizes and examination of single polymorphisms, further investigation may be warranted.

Norepinephrine Transporter Gene (*NET*; *SLC6A2*)

NET has been examined in ADHD due to the efficacy of drugs that block the norepinephrine transporter.^{54,55} Evi-

dence⁵⁴ has supported an association between 2 SNPs, the T allele (RR = 2.28) and the C allele (RR = 1.96). Evidence for association of an SNP in *NET* with ADHD symptoms was found in a sample of Tourette's syndrome patients.⁵⁶ However, a subsequent study⁵⁷ reported no association in the examination of 3 SNPs (located in exon 9, intron 9, and intron 13, respectively), their haplotypes, or loci in 122 ADHD families. A study⁵⁸ of Irish families found no association with intron 7 and intron 9 SNPs, while a family-based study⁵⁵ of adult offspring found no association with a RFLP. The norepinephrine transporter gene continues to be of interest in ADHD studies.

THE SEROTONERGIC SYSTEM

Serotonin Receptor Genes (*HTR1B* and *HTR2A*) and Serotonin Transporter Genes (*5-HTT*)

Three family-based association studies⁵⁹⁻⁶¹ examined a silent SNP (G861C) in the gene coding for the serotonin *HTR1B* receptor. An excess transmission of the 861G allele ($p = .052$) as well as the G/A haplotype ($p = .087$) was reported⁵⁹ in Chinese Han patients with inattentive ADHD, while the C/A haplotype was undertransmitted ($p = .054$). In comparison, in 2 predominantly Caucasian samples,^{59,61} overtransmission of the G allele was found. Faraone et al.² reported the pooled OR for the G861C SNP in these studies as 1.44 (95% CI = 1.14 to 1.83). However, a case-control quantitative trait locus analysis⁶² of 329 pairs of dizygotic male twins found no association between *HTR1B* and ADHD.

The serotonin transporter has also been examined in relation to ADHD. Two family-based studies^{63,64} reported overtransmission of the long allele of serotonin transporter gene-linked polymorphic region (HTTLPR), which was noted as consistent with case-control findings; however, the overtransmission reached statistical significance in neither study. Faraone et al.² stated that when the HTTLPR studies are combined, the pooled OR for the long allele is 1.31 (95% CI = 1.09 to 1.59), which is significant.

Tryptophan Hydroxylase Gene (*TPH*)

Enzymes that are responsible for the catalyzation of neurotransmitters are viable candidates for investigation, as they are often the rate-limiting step in the synthesis of catecholamines and indoleamines. As DBH is the rate-limiting enzyme involved in the synthesis of norepinephrine, so TPH is the rate-limiting enzyme involved in the synthesis of serotonin. *TPH* polymorphisms have been associated with aggression and impulsivity.⁶⁵ Family-based studies^{66,67} have noted that ADHD youths with learning disabilities showed an undertransmission of a haplotype composed of the 218A and 6526G alleles, despite the fact that neither SNP showed biased transmission individually. Thus, further study of *TPH* may be warranted.

OTHER CANDIDATE GENES

Acetylcholine Receptor Genes (*CHRNA4* and *CHRNA7*)

The nicotinic acetylcholine receptors are ligand-gated ion channels composed of 5 subunits. The α_4 subunit (*CHRNA4*) has been examined in 2 ADHD studies.^{68,69} Similar to other gene studies, family-based analyses of the gene have shown conflicting evidence. One study⁶⁸ found no significant evidence of association with the CfoI restriction site polymorphism (*CHRNA4*) in exon 5, while a larger study⁶⁹ of families ascertained from a twin sample did find an association between ADHD symptoms and *CHRNA4* polymorphisms. A family-based study⁷⁰ of 206 trios that examined the gene that codes for the α_7 subunit of the nicotinic acetylcholine receptor family (*CHRNA7*) found no association between ADHD and any of 3 repeat polymorphisms near this gene.

Glutamate Receptor Genes

Glutamatergic neurotransmission comprises the major excitatory system in the brain and is involved in the neuronal functions of fast synaptic transmission, neuronal migration, proliferation and excitability, synaptogenesis, stability, and plasticity.⁷¹ The ionotropic glutamate receptor gene (*GRIN2A*), which codes a subunit of the *N*-methyl-D-aspartate (NMDA) receptor, has been examined in cognition studies of both animals and humans.⁷² A family-based analysis⁷¹ of 238 families noted an SNP in exon 5 that was significantly associated with ADHD ($\chi^2 = 3.7$, $p = .04$) and haplotypes including additional SNPs that were weakly associated. However, a study⁷³ of 183 families noted no evidence for association for this SNP ($\chi^2 = 0.11$, $p = .74$) or 3 others.

Synaptosomal-Associated Protein 25 Gene (*SNAP25*)

The association of the synaptosomal-associated protein 25 gene (*SNAP25*) with ADHD is frequently studied in coloboma mouse models because these mice have the coloboma mutation, a hemizygous 2 centimorgan deletion of a segment on chromosome 2q. The mutation leads to spontaneous hyperactivity, delays in achieving complex neonatal motor abilities, and deficits in hippocampal physiology, which may contribute to learning deficiencies and deficits in Ca^{2+} -dependent dopamine release in the dorsal striatum.⁷⁴ Two biallelic SNPs of the *SNAP25* gene (T1069C and T1065G, separated by 4 bps at the 3' end of the gene) were examined in 4 family-based studies.⁷⁵⁻⁷⁸ A haplotype formed by these 2 adjacent SNPs revealed a significant association.⁷⁵ However, the largest study⁷⁷ of these SNPs did not detect an association but rather a slight predominance of paternal overtransmission of the haplotype implicated by the other studies. Mill et al.⁷⁸ conducted an examination of 8 polymorphisms composed of 2 microsatellites and 6 SNPs and concluded that 3 indi-

vidual markers were associated with ADHD. Discrepancies in association were noted between each of the *SNAP25* candidate gene studies that tested the same 2 adjacent SNPs. Despite these divergent findings, a pooled analysis² for the T1065G allele indicates significant evidence for an association with ADHD (OR = 1.19, 95% CI = 1.03 to 1.38).

Summary

Case-control and family-based studies have demonstrated that ADHD both has a complex genetic architecture and is a highly heritable condition. Many candidate gene studies have produced substantial evidence implicating several genes in the etiology of ADHD. By identifying variant genes in ADHD, we can further explore how genes influence medication response, which may lead to the development of targeted therapeutic agents.

PHARMACOGENETIC STUDIES

Pharmacogenetic studies investigate how gene variants influence medication response. Such studies have the potential to provide gene markers that predict medication efficacy, adverse events, or both. In addition, understanding how genes influence drug response helps clarify the biological mechanisms of disease pathogenesis. Pharmacogenetic studies seek to identify genetic patterns that will in turn lend insights into the developments of therapeutic agents. In the case of ADHD, the polygenic nature of the disorder and the clinical heterogeneity among patients may be better understood in the context of medications that reduce or ameliorate symptoms. Some of the most noteworthy clinical and preclinical pharmacogenetic studies are summarized in Table 2.⁷⁹⁻⁸⁷

Preclinical studies often provide insights into the pathophysiology of disease states. While preliminary findings from animal studies are not readily translated to a human model, the paradigm of gene expression is very useful in understanding medication effects in specified regions of the brain and helping to predict response and outcomes. Furthermore, safety profiles are established in preclinical models and early phase 1 drug development and are often the precursors to phase 1 research in human subjects. Such studies are useful not only in drug development but also in furthering the understanding of gene expression.

The *fos* family of intermediate early genes are present in brain tissue at low levels under basal conditions and are readily expressed in the presence of stimulants. Two of these intermediate early genes, *c-fos* and *fos-B*, may cause rapid versus long-term responses in regulating drug-induced neuroplasticity. In a rat model,⁸⁸ methylphenidate produced significant inhibitory expression changes in *c-fos* and increased *fos-B* expression in multiple brain regions. The long-term physiologic effects of acute or chronic *fos* expression in humans are unknown.

Table 2. Summary of Pharmacogenetics Studies

Study	N	Design	Outcome
Rohde et al, 2003 ⁷⁹	8	SPECT case control	<i>DAT</i> -10R associated with decreased extracellular dopamine
Loo et al, 2003 ⁸⁰	27	EEG case control	<i>DAT</i> -10R predicts methylphenidate associated changes in the EEG but not the continuous performance task
Stein et al, 2005 ⁸¹	47	Case control	<i>DAT</i> -9/9R less responsive to methylphenidate
Cheon et al, 2005 ⁸²	11	SPECT case control	<i>DAT</i> -10/10R showed increased basal ganglia <i>DAT</i> density and diminished methylphenidate response
Kirley et al, 2003 ⁸³	119	Retrospective family based	Receipt of <i>DAT</i> -10R from parent associated with favorable methylphenidate response
Hamarman et al, 2004 ⁸⁴	47	Case control	<i>DRD4</i> -7 associated with diminished methylphenidate response
Van der Meulen, 2003 ⁸⁵	82	Case control	Association trend for <i>DRD4</i> -7 and diminished methylphenidate response
Seeger et al, 2001 ⁸⁶	47	Case control	Increased prolactin with <i>DRD4</i> -7 and long allele of <i>5-HTT</i>
Yang et al, 2004 ⁸⁷	45	Case control	<i>NET</i> -A/A allele associated with diminished methylphenidate response

Abbreviations: 9R = 9-repeat allele, 10R = 10-repeat allele, *DAT* = dopamine transporter gene, *DRD4* = dopamine D₄ receptor gene, EEG = electroencephalogram, *5-HTT* = serotonin transporter gene, *NET* = norepinephrine transporter gene, SPECT = single-photon emission computed tomography.

In a case-control neonatal rat study,⁸⁹ rats received the neurotoxin 6-hydroxydopamine (6-OHDA), which causes lesions of dopamine neurons in the rat brain. On postnatal day 5, juvenile rats that had received 6-OHDA demonstrated markedly increased and sustained locomotor activity. Next, a human analog therapeutic dose of atomoxetine 1 mg/kg was administered IP. Within 35 minutes of atomoxetine administration, the control group showed a marked reduction in locomotor activity ($p = .05$) and the 6-OHDA-lesioned rats were indistinguishable from controls ($p = .001$). Atomoxetine ameliorated hyperactivity in 6-OHDA-lesioned rats and did not stimulate locomotor activity in controls, indicating a potential antidepressant-anxiolytic advantage over psychostimulants.

DISCUSSION

While many studies reviewed show comparable results, the divergence between candidate gene studies demonstrates the complex genetic architecture of ADHD. Many studies have produced significant results only to be challenged by other studies that do not. Heterogeneity between study designs can be readily observed in case-control, family-based analyses, ethnically stratified samples, statistical underpowering, and differences in phenotypic classification. The genetic vulnerability to ADHD may be an additive effect of many genes, each having relatively small effects. Therefore, studies that implement designs that lessen heterogeneity and provide adequate statistical power would be more likely to detect these small effects and contributory influences.

Many strong associations were found in catecholaminergic gene studies. *DRD4* was significantly associated with ADHD, yet several studies showed little or no association. The *DAT* 10-repeat polymorphisms have produced mixed findings ranging from strong associations and trends to no association, suggesting the need for replication and adequate statistical power. The *NET* and the α -adrenergic genes show promise, but the handful of stud-

ies indicative of trends needs to be replicated if any associations are to be determined. Positive findings from serotonergic gene studies further solidify the roles of *HTR1B* and *HTTLPR* in the pathogenesis of ADHD.

The evolving field of pharmacogenetics further elucidates the biological underpinnings of ADHD by allowing us to appreciate the genetic differences between patients. While studies have produced results implicating particular polymorphisms in decreased methylphenidate response, further replication is necessary before findings can be generalized to an entire population sample. Studies that employed similar methodologies were subject to divergent findings. Hamarman et al.,⁸⁴ for example, noted a strong association between the *DRD4*-7 allele and diminished methylphenidate response in a sample of 45 ADHD patients ($p = .0002$), while in another study with a similar design, Van der Meulen⁸⁵ noted a *DRD4*-7 trend in 86 ADHD patients that was not significant ($p = .086$). Similarly, case-control pharmacogenetic studies of the *DAT* 10-repeat allele yielded findings of diminished methylphenidate response, decreased regional cerebral blood flow, and cognitive impairment,^{79,80,82,83} while the 9-repeat allele was significantly associated in another study.⁸¹

The clinical implication of these association and pharmacogenetic studies will evolve in such a way as to help guide clinicians to diagnose and choose viable treatment options for their patients based on genetic profiles. Buccal-swab DNA collection has become a more prevalent method for noninvasive sample collection, and the advent of real-time polymerase chain reaction technology (cloning DNA) enables researchers to gather genetic profiles in a matter of hours. Furthermore, evolving technology, such as that offered in Affymetrix chips (Affymetrix, Santa Clara, Calif.), will allow researchers to examine and interpret 500,000 gene, haplotype, and microsatellite markers in each patient sample. Thus, the utilization of genetics as a means to understand disease states and assign viable treatments will be foundational in the future of clinical practice.

Drug names: amphetamine/dextroamphetamine (Adderall), atomoxetine (Strattera), dextroamphetamine (Dexedrine, Dextrostat, and others), methylphenidate (Ritalin, Concerta, and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

- Faraone SV, Spencer T, Aleardi M. Etiology and pathophysiology of adult attention deficit hyperactivity disorder. *Primary Psychiatry* 2004;11:28–40
- Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005;57:1313–1323
- Lowe N, Kirley A, Hawi Z, et al. Joint analysis of the DRD5 marker concludes association with attention-deficit/hyperactivity disorder confined to the predominantly inattentive and combined subtypes. *Am J Hum Genet* 2004;74:348–356
- Faraone SV, Biederman J. Neurobiology of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 1998;44:951–958
- Faraone SV, Doyle AE, Mick E, et al. Meta-analysis of the association between the 7-repeat allele of the dopamine D4 receptor gene and attentional deficit hyperactivity disorder. *Am J Psychiatry* 2001;158:1052–1057
- Rowe DC, Stever C, Chase D, et al. Two dopamine genes related to reports of childhood retrospective inattention and conduct disorder symptoms. *Mol Psychiatry* 2001;6:429–433
- Levitan RD, Masellis M, Lam RW, et al. Childhood inattention and dysphoria and adult obesity associated with the dopamine D4 receptor gene in overeating women with seasonal affective disorder. *Neuropsychopharmacology* 2004;29:179–186
- Daly G, Hawi Z, Fitzgerald M, et al. Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. *Mol Psychiatry* 1999;4:192–196
- Payton A, Holmes J, Barrett JH, et al. Examining for association between candidate gene polymorphisms in the dopamine pathway and attention-deficit hyperactivity disorder: a family-based study. *Am J Med Genet* 2001;105:464–470
- Barr CL, Wigg KG, Feng Y, et al. Attention-deficit hyperactivity disorder and the gene for the dopamine D5 receptor. *Mol Psychiatry* 2000;5:548–551
- Kustanovich V, Ishii J, Crawford L, et al. Transmission disequilibrium testing of dopamine-related candidate gene polymorphisms in ADHD: confirmation of association of ADHD with DRD4 and DRD5. *Mol Psychiatry* 2004;9:711–717
- Mill J, Curran S, Richards S, et al. Polymorphisms in the dopamine D5 receptor (DRD5) gene and ADHD. *Am J Med Genet B Neuropsychiatr Genet* 2004;125:38–42
- Maher BS, Marazita ML, Ferrell RE, et al. Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. *Psychiatr Genet* 2002;12:207–215
- Manor I, Corbex M, Eisenberg J, et al. Association of the dopamine D5 receptor with attention deficit hyperactivity disorder (ADHD) and scores on a continuous performance test (TOVA). *Am J Med Genet B Neuropsychiatr Genet* 2004;127:73–77
- Comings DE, Comings BG, Muhleman D, et al. The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. *JAMA* 1991;266:1793–1800
- Nierenberg AA, Miyahara S, Spencer T, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry* 2005;57:1467–1473
- Spencer T, Biederman J, Wilens T. Pharmacotherapy of attention deficit hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 2000;9:77–97
- Giros B, Jaber M, Jones S, et al. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature* 1996;379:606–612
- Gainetdinov RR, Jones SR, Caron MG. Functional hyperdopaminergia in dopamine transporter knock-out mice. *Biol Psychiatry* 1999;46:303–311
- Zhuang X, Oosting RS, Jones SR, et al. Hyperactivity and impaired response habituation in hyperdopaminergic mice. *Proc Natl Acad Sci U S A* 2001;98:1982–1987
- Cook EH Jr, Stein MA, Krasowski MD, et al. Association of attention-deficit disorder and the dopamine transporter gene. *Am J Hum Genet* 1995;56:993–998
- Curran S, Mill J, Tahir E, et al. Association study of a dopamine transporter polymorphism and attention deficit hyperactivity disorder in UK and Turkish samples. *Mol Psychiatry* 2001;6:425–428
- Todd RD, Jong YJ, Lobos EA, et al. No association of the dopamine transporter gene 3' VNTR polymorphism with ADHD subtypes in a population sample of twins. *Am J Med Genet* 2001;105:745–748
- Chen CK, Chen SL, Mill J, et al. The dopamine transporter gene is associated with attention deficit hyperactivity disorder in a Taiwanese sample. *Mol Psychiatry* 2003;8:393–396
- Payton A, Holmes J, Barrett JH, et al. Susceptibility genes for a trait measure of attention deficit hyperactivity disorder: a pilot study in a non-clinical sample of twins. *Psychiatry Res* 2001;105:273–278
- Smith KM, Daly M, Fischer M, et al. Association of the dopamine beta hydroxylase gene with attention deficit hyperactivity disorder: genetic analysis of the Milwaukee longitudinal study. *Am J Med Genet B Neuropsychiatr Genet* 2003;119:77–85
- Bakker SC, Van der Meulen EM, Oteman N, et al. DAT1, DRD4, and DRD5 polymorphisms are not associated with ADHD in Dutch families. *Am J Med Genet B Neuropsychiatr Genet* 2005;132:50–52
- Mill J, Xu X, Ronald A, et al. Quantitative trait locus analysis of candidate gene alleles associated with attention deficit hyperactivity disorder (ADHD) in five genes: DRD4, DAT1, DRD5, SNAP-25, and 5HT1B. *Am J Med Genet B Neuropsychiatr Genet* 2005;133:68–73
- Waldman ID, Rowe DC, Abramowitz A, et al. Association and linkage of the dopamine transporter gene and attention-deficit hyperactivity disorder in children: heterogeneity owing to diagnostic subtypes and severity. *Am J Hum Genet* 1998;63:1767–1776
- Muglia P, Jain U, Inkster B, et al. A quantitative trait locus analysis of the dopamine transporter gene in adults with ADHD. *Neuropsychopharmacology* 2002;27:655–662
- Roman T, Martins S, Szobot C, et al. Dopamine transporter gene and response to methylphenidate in ADHD. *Pharmacogenetics* 2002;12:497–499
- Wigg K, Zai G, Schachar R, et al. Attention deficit hyperactivity disorder and the gene for dopamine beta-hydroxylase. *Am J Psychiatry* 2002;159:1046–1048
- Hawi Z, Lowe N, Kirley A, et al. Linkage disequilibrium mapping at DAT1, DRD5 and DBH narrows the search for ADHD susceptibility alleles at these loci. *Mol Psychiatry* 2003;8:299–308
- Barr CL, Wigg KG, Bloom S, et al. Further evidence from haplotype analysis for linkage of the dopamine D4 receptor gene and attention-deficit hyperactivity disorder. *Am J Med Genet* 2000;96:262–267
- Comings DE, Gade R, Muhleman D, et al. No association of a tyrosine hydroxylase gene tetranucleotide repeat polymorphism in autism, Tourette syndrome, or ADHD. *Biol Psychiatry* 1995;37:484–486
- Barr CL, Wigg K, Malone M, et al. Linkage study of catechol-O-methyltransferase and attention-deficit hyperactivity disorder. *Am J Med Genet* 1999;88:710–713
- Hawi Z, Millar N, Daly G, et al. No association between catechol-O-methyltransferase (COMT) gene polymorphism and attention deficit hyperactivity disorder (ADHD) in an Irish sample. *Am J Med Genet* 2000;96:282–284
- Manor I, Kotler M, Sever Y, et al. Failure to replicate an association between the catechol-O-methyltransferase polymorphism and attention deficit hyperactivity disorder in a second, independently recruited Israeli cohort. *Am J Med Genet* 2000;96:858–860
- Tahir E, Curran S, Yazgan Y, et al. No association between low- and high-activity catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD) in a sample of Turkish children. *Am J Med Genet* 2000;96:285–288
- Eisenberg J, Mei-Tal G, Steinberg A, et al. Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): association of the high-enzyme activity Val allele with ADHD impulsive-hyperactive phenotype. *Am J Med Genet* 1999;88:497–502
- Qian Q, Wang Y, Zhou R, et al. Family-based and case-control association studies of catechol-O-methyltransferase in attention deficit hyperactivity disorder suggest genetic sexual dimorphism. *Am J Med Genet B Neuropsychiatr Genet* 2003;118:103–109
- Cases O, Lebrand C, Giros B, et al. Plasma membrane transporters of serotonin, dopamine, and norepinephrine mediate serotonin accumulation in atypical locations in the developing brain of monoamine oxidase A knock-outs. *J Neurosci* 1998;18:6914–6927
- Domschke K, Sheehan K, Lowe N, et al. Association analysis of the monoamine oxidase A and B genes with attention deficit hyperactivity disorder (ADHD) in an Irish sample: preferential transmission of the MAO-A 941G allele to affected children. *Am J Med Genet B Neuropsychiatr Genet* 2005;134:110–114
- Manor I, Tyano S, Mel E, et al. Family-based and association studies of monoamine oxidase A and attention deficit hyperactivity disorder (ADHD):

- preferential transmission of the long promoter-region repeat and its association with impaired performance on a continuous performance test (TOVA). *Mol Psychiatry* 2002;7:626–632
45. Jiang S, Xin R, Lin S, et al. Linkage studies between attention-deficit hyperactivity disorder and the monoamine oxidase genes. *Am J Med Genet* 2001;105:783–788
 46. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 2002;27:699–711
 47. Comings DE, Chen C, Wu S, et al. Association of the androgen receptor gene (AR) with ADHD and conduct disorder. *Neuroreport* 1999;10:1589–1592
 48. Comings DE, Gonzalez NS, Cheng Li SC, et al. A “line item” approach to the identification of genes involved in polygenic behavioral disorders: the adrenergic alpha2A (ADRA2A) gene. *Am J Med Genet B Neuropsychiatr Genet* 2003;118:110–114
 49. Xu C, Schachar R, Tannock R, et al. Linkage study of the alpha2A adrenergic receptor in attention-deficit hyperactivity disorder families. *Am J Med Genet* 2001;105:159–162
 50. Roman T, Schmitz M, Polanczyk GV, et al. Is the alpha-2A adrenergic receptor gene (ADRA2A) associated with attention-deficit/hyperactivity disorder? *Am J Med Genet B Neuropsychiatr Genet* 2003;120:116–120
 51. Barr CL, Wigg K, Zai G, et al. Attention-deficit hyperactivity disorder and the adrenergic alpha 1C and alpha 2C. *Mol Psychiatry* 2001;6:334–337
 52. De Luca V, Muglia P, Vincent JB, et al. Adrenergic alpha 2C receptor genomic organization: association study in adult ADHD. *Am J Med Genet B Neuropsychiatr Genet* 2004;127:65–67
 53. Comings DE, Gade-Andavolu R, Gonzalez N, et al. Additive effect of three noradrenergic genes (ADRA2A, ADRA2C, DBH) on attention-deficit hyperactivity disorder and learning disabilities in Tourette syndrome subjects. *Clin Genet* 1999;55:160–172
 54. Bobb AJ, Addington AM, Sidransky E, et al. Support for association between ADHD and two candidate genes: NET1 and DRD1. *Am J Med Genet B Neuropsychiatr Genet* 2005;134:67–72
 55. De Luca V, Muglia P, Jain U, et al. No evidence of linkage or association between the norepinephrine transporter (NET) gene MnlII polymorphism and adult ADHD. *Am J Med Genet B Neuropsychiatr Genet* 2004;124:38–40
 56. Comings DE. Clinical and molecular genetics of ADHD and Tourette syndrome: two related polygenic disorders. *Ann N Y Acad Sci* 2001;931:50–83
 57. Barr CL, Kroft J, Feng Y, et al. The norepinephrine transporter gene and attention-deficit hyperactivity disorder. *Am J Med Genet* 2002;114:255–259
 58. McEvoy B, Hawi Z, Fitzgerald M, et al. No evidence of linkage or association between the norepinephrine transporter (NET) gene polymorphisms and ADHD in the Irish population [letter]. *Am J Med Genet* 2002;114:665–666
 59. Li J, Wang Y, Zhou R, et al. Serotonin 5-HT1B receptor gene and attention deficit hyperactivity disorder in Chinese Han subjects. *Am J Med Genet B Neuropsychiatr Genet* 2005;132:59–63
 60. Hawi Z, Dring M, Kirley A, et al. Serotonergic system and attention deficit hyperactivity disorder (ADHD): a potential susceptibility locus at the 5-HT (1B) receptor gene in 273 nuclear families from a multi-centre sample. *Mol Psychiatry* 2002;7:718–725
 61. Quist JF, Barr CL, Schachar R, et al. The serotonin 5-HT1B receptor gene and attention deficit hyperactivity disorder. *Mol Psychiatry* 2003;8:98–102
 62. Yanagita T, Miyasato K. Dependence potential of methaqualone tested in rhesus monkeys. *CIEA Preclin Rep* 1976;2:63–68
 63. Manor I, Eisenberg J, Tyano S, et al. Family-based association study of the serotonin transporter promoter region polymorphism (5-HTTLPR) in attention deficit hyperactivity disorder. *Am J Med Genet* 2001;105:91–95
 64. Kent L, Doerry U, Hardy E, et al. Evidence that variation at the serotonin transporter gene influences susceptibility to attention deficit hyperactivity disorder (ADHD): analysis and pooled analysis. *Mol Psychiatry* 2002;7:908–912
 65. Manuck SB, Flory JD, Ferrell RE, et al. Aggression and anger-related traits associated with a polymorphism of the tryptophan hydroxylase gene. *Biol Psychiatry* 1999;45:603–614
 66. Tang G, Ren D, Xin R, et al. Lack of association between the tryptophan hydroxylase gene A218C polymorphism and attention-deficit hyperactivity disorder in Chinese Han population. *Am J Med Genet* 2001;105:485–488
 67. Li J, Wang YF, Zhou RL, et al. Association between tryptophan hydroxylase gene polymorphisms and attention deficit hyperactivity disorder with or without learning disorder [in Chinese]. *Zhonghua Yi Xue Za Zhi* 2003;83:2114–2118
 68. Kent L, Middle F, Hawi Z, et al. Nicotinic acetylcholine receptor alpha 4 subunit gene polymorphism and attention deficit hyperactivity disorder. *Psychiatr Genet* 2001;11:37–40
 69. Todd RD, Lobos EA, Sun LW, et al. Mutational analysis of the nicotinic acetylcholine receptor alpha 4 subunit gene in attention deficit/hyperactivity disorder: evidence for association of an intronic polymorphism with attention problems. *Mol Psychiatry* 2003;8:103–108
 70. Kent L, Green E, Holmes J, et al. No association between CHRNA7 microsatellite markers and attention-deficit hyperactivity disorder. *Am J Med Genet* 2001;105:686–689
 71. Turic D, Langley K, Mills S, et al. Follow-up of genetic linkage findings on chromosome 16p13: evidence of association of N-methyl-D aspartate glutamate receptor 2A gene polymorphism with ADHD. *Mol Psychiatry* 2004;9:169–173
 72. Smalley SL, Kustanovich V, Minassian SL, et al. Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism. *Am J Hum Genet* 2002;71:959–963
 73. Adams J, Crosbie J, Wigg K, et al. Glutamate receptor, ionotropic, N-methyl D-aspartate 2A (GRIN2A) gene as a positional candidate for attention-deficit/hyperactivity disorder in the 16p13 region. *Mol Psychiatry* 2004;9:494–499
 74. Wilson MC. Coloboma mouse mutant as an animal model of hyperkinesia and attention deficit hyperactivity disorder. *Neurosci Biobehav Rev* 2000;24:51–57
 75. Barr CL, Feng Y, Wigg K, et al. Identification of DNA variants in the SNAP-25 gene and linkage study of these polymorphisms and attention-deficit hyperactivity disorder. *Mol Psychiatry* 2000;5:405–409
 76. Brophy K, Hawi Z, Kirley A, et al. Synaptosomal-associated protein 25 (SNAP-25) and attention deficit hyperactivity disorder (ADHD): evidence of linkage and association in the Irish population. *Mol Psychiatry* 2002;7:913–917
 77. Kustanovich V, Merriman B, McGough J, et al. Biased paternal transmission of SNAP-25 risk alleles in attention-deficit hyperactivity disorder. *Mol Psychiatry* 2003;8:309–315
 78. Mill J, Richards S, Knight J, et al. Haplotype analysis of SNAP-25 suggests a role in the aetiology of ADHD. *Mol Psychiatry* 2004;9:801–810
 79. Rohde LA, Roman T, Szobot C, et al. Dopamine transporter gene, response to methylphenidate and cerebral blood flow in attention-deficit/hyperactivity disorder: a pilot study. *Synapse* 2003;48:87–89
 80. Loo SK, Specter E, Smolen A, et al. Functional effects of the DAT1 polymorphism on EEG measures in ADHD. *J Am Acad Child Adolesc Psychiatry* 2003;42:986–993
 81. Stein MA, Waldman ID, Sarampote CS, et al. Dopamine transporter genotype and methylphenidate dose response in children with ADHD. *Neuropsychopharmacology* 2005;30:1374–1382
 82. Cheon K, Ryu YH, Kim JW, et al. The homozygosity for 10-repeat allele at dopamine transporter gene and dopamine transporter density in Korean children with attention deficit hyperactivity disorder: relating to treatment response to methylphenidate. *Eur Neuropsychopharmacol* 2005;15:95–101
 83. Kirley A, Lowe N, Hawi Z, et al. Association of the 480 bp DAT1 allele with methylphenidate response in a sample of Irish children with ADHD. *Am J Med Genet B Neuropsychiatr Genet* 2003;121:50–54
 84. Hamarman S, Fossella L, Ulger C, et al. Dopamine receptor 4 (DRD4) 7-repeat allele predicts methylphenidate dose response in children with attention deficit hyperactivity disorder: a pharmacogenetic study. *J Child Adolesc Psychopharmacol* 2004;14:564–574
 85. Van der Meulen E. Attention deficit hyperactivity disorder in Dutch children: a family study of genotype, phenotype, and environment [dissertation]. The Netherlands: Utrecht University Medical Center; June 2003
 86. Seeger G, Schloss P, Schmidt MH. Marker gene polymorphisms in hyperkinetic disorder: predictors of clinical response to treatment with methylphenidate? *Neurosci Lett* 2001;313:45–48
 87. Yang L, Wang Y-F, Li J, et al. Association of norepinephrine transporter gene with methylphenidate response. *J Am Acad Child Adolesc Psychiatry* 2004;43:1154–1158
 88. Chase TD, Carrey N, Brown RE, et al. Methylphenidate regulates *c-fos* and *fos-B* expression in multiple regions of the immature rat brain. *Brain Res Dev Brain Res* 2005;156:1–12
 89. Moran-Gates T, Zhang K, Baldessarini RJ, et al. Atomoxetine blocks motor hyperactivity in neonatal 6-hydroxydopamine-lesioned rats: implications for treatment of attention-deficit hyperactivity disorder. *Int J Neuropsychopharmacol* 2005;8:439–444