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 D_4 receptor gene (*DRD4*), the dopamine D_5 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 relevant 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
SNAP25 (T1065G)	Family	1.19	1.03 to 1.38
Serotonin transporter (5-HTTLPR long)	Case control	1.31	1.09 to 1.59
HTR1B (G861C)	Family	1.44	1.14 to 1.83

[a]Reprinted with permission from Faraone et al.[2] OR and CI values were computed by Faraone et al.[2]
[b]Data 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 D_4 receptor gene (*DRD4*), the dopamine D_5 receptor gene (*DRD5*), and the dopamine transporter gene (*DAT*).

Dopamine D_4 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 D_5 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 study[9] of 81 families from the United Kingdom showed no evidence for an association with the dinucleotide repeat polymorphism. In addition, a Canadian study[10] 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 study[12] 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-analysis[13] 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 analysis[3] 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 study[14] that was not limited to inattentive and combined subtypes.

Dopamine D_2 Receptor Gene (*DRD2*)

DRD2 has been studied less extensively in ADHD than *DRD4* and *DRD5*. A case-control study[15] of patients with ADHD (mostly comorbid with Tourette's disorder) found an association with the TaqI A1 allele of *DRD2*. Conversely, a family-based study[16] 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 D_3 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 findings[20] 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-analysis[22] showed a small positive, but nonsignificant, OR of 1.16, which was suggestive of significant heterogeneity among data sets. A second meta-analysis[13] utilized 11 family-based samples (9 of which were part of the first meta-analysis[22]) but revealed a nonsignificant OR of 1.27. Subsequent to the publication of the 2 meta-analyses, several additional studies[23–27] have appeared in the literature, many of them involving family-based twin samples, but with divergent results. Other studies[28–30] 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 severity[29] 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 study[26] and family-based studies[8,31] have supported an association between *DBH* and ADHD. The logistic regression analysis used in the case-control study[26] 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 study[8] 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 study[31] 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 study[40] subsequently corrected their report to include less overtransmission of the Val allele than was originally reported, pooled analysis[2] of these

studies showed no evidence of an association between ADHD and *COMT* (OR = 1.0, p = 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 study[43] 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 analyses[43] 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 study[44] 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] Evidence[54] 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 study[57] 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 study[58] of Irish families found no association with intron 7 and intron 9 SNPs, while a family-based study[55] 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 studies[59–61] 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 reported[59] 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 analysis[62] 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 study[68] found no significant evidence of association with the CfoI restriction site polymorphism (*CHRNA4*) in exon 5, while a larger study[69] of families ascertained from a twin sample did find an association between ADHD symptoms and *CHRNA4* polymorphisms. A family-based study[70] 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 analysis[71] 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 study[73] 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 study[77] 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 individual 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 analysis[2] 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	*DAT*-10R associated with decreased extracellular dopamine
Loo et al, 2003[80]	27	EEG case control	*DAT*-10R predicts methylphenidate associated changes in the EEG but not the continuous performance task
Stein et al, 2005[81]	47	Case control	*DAT*-9/9R less responsive to methylphenidate
Cheon et al, 2005[82]	11	SPECT case control	*DAT*-10/10R showed increased basal ganglia DAT density and diminished methylphenidate response
Kirley et al, 2003[83]	119	Retrospective family based	Receipt of *DAT*-10R from parent associated with favorable methylphenidate response
Hamarman et al, 2004[84]	47	Case control	*DRD4–7* associated with diminished methylphenidate response
Van der Meulen, 2003[85]	82	Case control	Association trend for *DRD4–7* and diminished methylphenidate response
Seeger et al, 2001[86]	47	Case control	Increased prolactin with *DRD4–7* and long allele of *5-HTT*
Yang et al, 2004[87]	45	Case control	*NET*-A/A allele associated with diminished methylphenidate response

Abbreviations: 9R = 9-repeat allele, 10R = 10-repeat allele, *DAT* = dopamine transporter gene, *DRD4* = dopamine D_4 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 studies 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 Meulen[85] 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 (Straterra), 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.

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