Molecular Genetics of Attention-Deficit/Hyperactivity Disorder

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Results of behavioral genetic and molecular genetic studies have converged to suggest that both genetic and nongenetic factors contribute to the development of attention-deficit/hyperactivity disorder (ADHD). We review this literature, with a particular emphasis on molecular genetic studies. Family, twin, and adoption studies provide compelling evidence that genes play a strong role in mediating susceptibility to ADHD. This fact is most clearly seen in the 20 extant twin studies, which estimate the heritability of ADHD to be .76. Molecular genetic studies suggest that the genetic architecture of ADHD is complex. The few genome-wide scans conducted thus far are 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 eight genes for which the same variant has been studied in three or more case–control or family-based studies, seven show statistically significant evidence of association with ADHD on the basis of the pooled odds ratio across studies: DRD4, DRD5, DAT, DBH, 5-HTT, HTR1B, and SNAP-25.

Key Words: ADHD, genetics, linkage, candidate genes, twins

With a prevalence of 8%–12% worldwide (Faraone et al 2003), attention-deficit/hyperactivity disorder (ADHD) is among the most common childhood psychiatric disorders. Its name reflects the range of possible clinical presentations, which can include hyperactivity as well as inattention and impulsivity (Wilens et al 2002). In spite of this heterogeneity and some shift in diagnostic criteria (American Psychiatric Association 1987), it is also among the best-validated childhood diagnoses from both clinical and neurobiological perspectives (Faraone and Biederman 1998; Faraone et al 2000b). This feature, along with early observations that family members of children with ADHD were at elevated risk for ADHD (Morrison and Stewart 1971), made ADHD an attractive target for genetic studies. In this review, we examine evidence showing that ADHD is strongly influenced by genes and review the progress of molecular genetic studies seeking to find these genes and the variants that increase susceptibility to ADHD.

Family, Twin, and Adoption Studies of ADHD

Several studies have reported an elevated prevalence of ADHD among family members of individuals with ADHD (here and elsewhere we use the term "ADHD" to refer to current and prior terms used to describe the syndrome). Early studies found the risk of ADHD among parents of children with ADHD to be increased by two- to eightfold, with similarly elevated risk among the siblings of ADHD subjects (for a review of this literature, see Faraone and Biederman 2000). Because other environmental differences could account for elevated risk, two double-blind, case–control studies specifically examined the risk to siblings of ADHD children when environmental factors are considered as well (Biederman et al 1990, 1992; Faraone et al 1992, 2000a). After controlling for gender, intactness of family, and socioeconomic status, these studies confirmed the familiality of ADHD.

Because, in the absence of molecular genetic data, family studies cannot disentangle genetic from environmental sources of transmission, we turn to adoption and twin studies to determine whether genes account for the familial transmission of a disorder. If genes contribute significantly to ADHD risk, biological relatives of ADHD children should be at greater risk for ADHD than adoptive relatives of adopted ADHD children. Two studies found that biological relatives of hyperactive children were more likely to have hyperactivity than adoptive relatives (Cantwell 1975; Morrison and Stewart 1973). A more recent study likewise found rates of ADHD to be greater among biological relatives of nonadopted ADHD children than adoptive relatives of adopted ADHD children (Sprich et al 2000). The adoptive relatives had a risk for ADHD similar to the risk in relatives of control children.

A more direct method of examining the heritability of ADHD is to study twins: monozygotic ("identical") twins share essentially 100% of their genes, whereas dizygotic ("fraternal") twins, like other siblings, share 50% of their genes. The extent to which identical twins are more concordant for ADHD than fraternal twins can be used to compute heritability, which is the degree to which variability in ADHD in the population can be accounted for by genes. Figure 1 shows estimates of heritability from 20 twin studies from the United States, Australia, Scandinavia, and the European Union: the mean heritability estimate of 76% shows that ADHD is among the most heritable of psychiatric disorders (Coolidge et al 2000; Edelbrock et al 1992; Gillis et al 1992; Gjone et al 1996; Goodman and Stevenson 1989; Hudziak et al 2000; Levy et al 1997; Martin et al 2002; Matheny and Brown 1971; Nadder et al 1998; Rietveld et al 2003; Schmitz et al 1995; Sherman et al 1997; Silberg et al 1996; Stevenson 1992; Thapar et al 1995; Thapar et al 2000; Willcutt et al 2000; Willerman 1973).

Molecular Genetic Studies of ADHD

In an attempt to find regions of chromosomes that might harbor genes for ADHD, three groups have conducted genome-wide linkage scans. By this approach, many DNA acid markers across the genome are examined to determine whether any

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Received June 2, 2004; revised October 14, 2004; accepted November 10, 2004.

0006-3223/05/$30.00
doi:10.1016/j.biopsych.2004.11.024

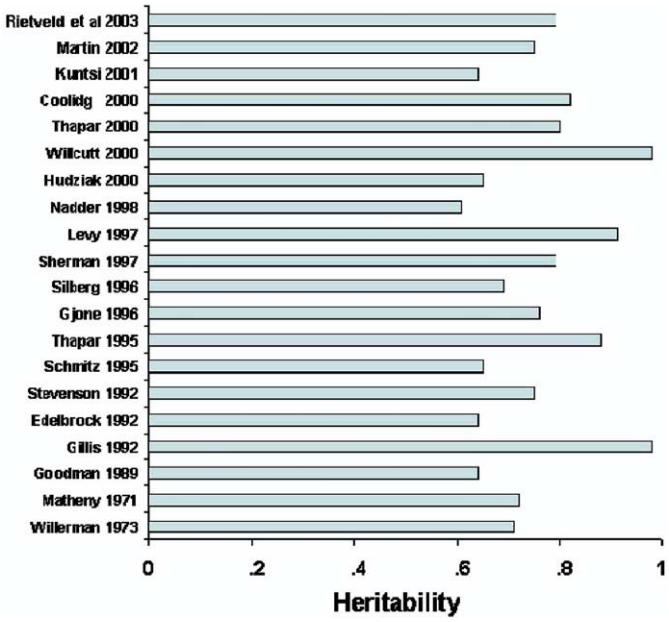

Figure 1. Estimated heritability of attention-deficit/hyperactivity disorder, based on pooled results from 20 twin studies.

chromosomal regions are shared more often than expected among ADHD family members. Regions identified in these studies can then be examined in more detail with additional markers.

A study of 126 American affected sib-pairs found four regions showing some evidence of linkage (log odds ratio [LOD] scores >1.5): 5p12, 10q26, 12q23, and 16p13 (Fisher et al 2002). An expanded sample of 203 families found stronger evidence for the 16p13 region, previously implicated in autism, with a maximum LOD score of 4 (Smalley et al 2002). A study of 164 Dutch affected sib-pairs also identified a peak previously noted in autism, at 15q15, with a peak LOD score of 3.5 (Bakker et al 2003). Two other peaks, at 7p13 and 9q33, yielded LOD scores of 3.0 and 2.1, respectively. A genome-wide scan of families from a genetically isolated community in Colombia implicated 8q12, 11q23, 4q13, 17p11, 12q23, and 8p23 (Arcos-Burgos et al 2004). With the exception of 17p11, genomic regions implicated by these studies do not overlap. Nevertheless, given that these studies individually had low power to detect linkage to genes of small effect, these regions remain of interest for replication studies and for fine mapping efforts.

In contrast to the scarcity of linkage studies, many candidate gene studies have used the method of association to determine whether biologically relevant genes influence the susceptibility to ADHD. In these studies, investigators choose genes on the basis of neurobiological studies or theoretical considerations suggesting that the gene product is relevant to the etiology of ADHD. Candidate gene studies have used case–control or family-based designs. Case–control designs compare allele frequencies between patients with ADHD and non-ADHD control subjects. Alleles that confer risk for ADHD should be more common among ADHD patients. The family-based design compares the alleles that parents transmit to ADHD children with those 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. From both study designs, it is possible to derive an odds ratio (OR) or relative risk (RR) statistic, which assesses the magnitude of the association between ADHD and the putative risk alleles (an OR or RR of 1.0 indicate no association, those greater than 1.0 indicate that the allele increases risk for ADHD, and those less than 1.0 indicate that the allele decreases the risk for ADHD). In the following section, we summarize the candidate gene results from these two study designs and, to facilitate the interpretation of results, we compute pooled ORs across studies for gene variants examined in three or more case–control or family-based studies.

Catecholaminergic Genes

The Dopamine D4 Receptor. Both noradrenaline and dopamine are potent agonists of the dopamine D4 receptor (DRD4) (Lanau et al 1997), and DRD4 is prevalent in frontal–subcortical networks implicated in the pathophysiology of ADHD by neuroimaging and neuropsychological studies (Faraone and Biederman 1998). Researchers have predominantly focused on a tandem repeat polymorphism in exon III of DRD4 because in vitro studies have shown that one variant (the 7-repeat allele) produces a blunted response to dopamine (Asghari et al 1995; Van Tol et al 1992).

Faraone et al (2001b) examined the ADHD–DRD4 association in meta-analyses of both case–control and family-based association studies. In each analysis, a small but statistically significant association emerged between ADHD and the 7-repeat allele. For case–control studies, the combined estimate of the OR was 1.9 (95% confidence interval [CI] 1.4–2.2). For family-based studies, the combined estimate was 1.4 (95% CI 1.1-1.6). There was no evidence for heterogeneity of the OR across studies, no evidence that a single study accounted for the significance or magnitude of the association, and no evidence for publication bias for either study design.

In more recent studies, positive case–control associations with DRD4-7 have been documented in reports from the United States (Grady et al 2003) and Brazil (Roman et al 2001), although in this latter study, a family-based analysis with 49 triads did not show biased transmission. A family-based study from the United Kingdom and Ireland also found evidence for the association between ADHD and DRD4-7 (Holmes et al 2002). Other recent studies have been unable to document significant associations with DRD4-7 but have still found ORs greater than 1.0. Payton et al (2001b) found a nonsignificant association between the 7-repeat allele and high scores on the DuPaul ADHD rating scale (OR 1.4; 95% CI .6–2.9) in a population-based twin sample. Additionally, a family study in a genetically isolated community in Colombia reported a near-significant association of DRD4-7 and ADHD (Arcos-Burgos et al 2004).

Yet, divergent findings have also been reported. Mill et al (2001) found no evidence for biased transmission of the 7-repeat allele in a family-based analysis of DSM-III attention-deficit disorder. Kustanovich et al (2003a) expanded an earlier family study and found no significant association between ADHD and the 7-repeat allele. A case–control study of Han Chinese found no ADHD or control subjects with the 7-repeat allele. This study found no overall association of any allele with ADHD, although longer alleles (4 through 6) were more common in ADHD than control subjects after stratification by gender (Qian et al 2003a). Interestingly, Manor et al (2002a) found an excess of short alleles (i.e., 2–5 repeats) in ADHD cases from an Israeli sample and biased transmission of the short alleles in a family-based analysis. Subjects with short alleles also performed more poorly on a continuous performance test. In an American sample, Smith and colleagues (Smith KM et al 2003) found a trend toward a lower

prevalence of the 4-repeat allele in ADHD subjects due to an excess of 2- and 3-repeat alleles. Results of these latter two studies raise the possibility of allelic heterogeneity in DRD4 or suggest that the Exon III polymorphism is in linkage disequilibrium with the true risk allele. Despite these divergent findings, when all studies of the exon III polymorphism are pooled, the association with ADHD remains statistically significant: case–control OR = 1.45 (95% CI 1.27–1.65); family based OR = 1.16 (95% CI 1.03–1.31).

A small number of studies have assessed other DRD4 polymorphisms; however, these data have not been conclusive. McCracken and colleagues (Kustanovich et al 2003a; McCracken et al 2000) found an association between ADHD and a 120-base pair (bp) repeat 1.2 kilobases (kb) upstream of the initiation codon, in the promoter. The association with the 240 allele was strongest for the Inattentive subtype; however, Barr et al (2001a) found no association between ADHD and three polymorphisms in the promoter region, including the 120-bp repeat and two single nucleotide polymorphisms (SNPs) (FspI -521 C to T and Ava –II -616 C to G). Todd et al (2001b) also found no association between the 5′120-bp repeat and ADHD as well as seven latent classes based on ADHD symptoms. Most recently, this 5′120-bp repeat was significantly associated with ADHD only when the 240 allele was included with the 7-repeat allele in a haplotype analysis (Arcos-Burgos et al 2004).

Studies using symptom dimensions rather than categoric diagnoses suggest that DRD4 might be particularly relevant to symptoms of inattention. Rowe et al (2001) found that fathers of ADHD children with the 7-repeat allele had higher levels of retrospectively reported inattention symptoms, and Levitan et al (2004) found an association between this allele and greater self-reported childhood inattention in women with seasonal affective disorder.

The Dopamine D5 Receptor. The most widely studied polymorphism for the dopamine D5 receptor (DRD5) has been a dinucleotide repeat that maps approximately 18.5 kb 5′ to the transcription start site (Hawi et al 2003). In a study of 111 Irish families, Daly et al (1999) found excess transmission of the 148-bp allele to ADHD patients. The effect was strongest among families without parental history of ADHD. Modest support for this association was seen in a sample of 111 Turkish families (Tahir et al 2000b) and in a case–control sample of Tourette's syndrome children with symptoms of ADHD (Comings et al 2000b). In contrast, a study of 81 families from the United Kingdom found no evidence for an association with the dinucleotide repeat polymorphism (Payton et al 2001a), and a Canadian study found no significant association with the 148-bp allele but significant under-transmission of the 146-bp allele (Barr et al 2000c), which was also reported by an American group (Kustanovich et al 2003a). Another study of three markers found an association only for a downstream dinucleotide repeat not assessed in other studies (Mill et al 2004a).

Despite the variability of these results, a meta-analysis of family-based studies found a significant association with DRD5 in ADHD, suggesting that the nonsignificant findings were due to low statistical power (Maher et al 2002). Consistent with this result, a more recent family-based analysis that combined 14 independent samples identified a significant association of the 148-bp allele with ADHD (OR = 1.2; 95% CI 1.1–1.4) (Lowe et al 2004), as did another family-based replication study (Manor et al 2004). Of note, Lowe et al's association was limited to the inattentive and combined subtypes.

Hawi et al (2003) expanded analyses of the Irish sample to include two additional 5′ microsatellite markers (further upstream than the dinucleotide repeat described above) and an SNP in the 3′ untranslated region. The 3′ SNP was associated with ADHD (RR = 1.6). In addition, haplotype analyses showed an association with ADHD for a two-marker haplotype of one of the 5′ microsatellite markers (D4S1582) and the dinucleotide repeat (DRD5-PCR1), as well as a different two-marker haplotype comprising DRD5-PCR1 and the 3′ SNP, and a haplotype comprising all three of these markers.

The Dopamine D2 Receptor. The dopamine D2 receptor (DRD2) has been less extensively studied in ADHD than DRD4 and DRD5. Comings et al (1991)compared 104 ADHD subjects (nearly all with comorbid Tourette's syndrome) with control subjects and found a significant association with the TaqIA1 allele of DRD2. This result was replicated in a subsequent study by the same group (Comings et al 1996a).

Three studies used a family-based design to examine DRD2. Rowe et al (1999) examined 164 ADHD children from 125 families and found no excess transmission of the Taq1A1 allele. A subsequent study of Taiwanese families likewise found no association (Huang et al 2003). Kirley et al (2002) examined two polymorphisms in 118 ADHD children and their families. No significant associations were identified, though they reported a trend toward significance ($p = .07$) for the Ser311 polymorphism when paternally transmitted. The discordance between family-based and case–control studies here might relate to differences in study populations, because the positive studies examined subjects with comorbid Tourette's syndrome (Comings et al 1991, 1996a). On aggregate, the studies to date suggest little or no association with ADHD.

The Dopamine D3 Receptor. Barr et al (2000d) examined a Ser9Gly exon 1 polymorphism and an intron 5 MspI restriction site polymorphism in 100 Canadian families. The two loci were found to be in strong linkage disequilibrium, but neither the individual loci nor haplotypes of the two were associated with ADHD. Negative results for the Ser9Gly polymorphism were also reported in a United Kingdom family-based study of 105 families (Payton et al 2001a) and a study of 39 families of ADHD adults (Muglia et al 2002b). In their Tourette's syndrome sample, Comings et al (2000b) also found no evidence for association. In a sample of 146 German patients referred for forensic evaluation (Retz et al 2003), heterozygosity at this polymorphism was associated with higher impulsivity scores, although this effect was only seen among those with a history of violence. When all extant studies are combined, the pooled OR (1.2) is not statistically significant.

The Dopamine Transporter Gene. There are several reasons that the dopamine transporter gene (DAT, SLC6A3) has been considered a suitable candidate for ADHD. The stimulant medications, which are efficacious in treating ADHD, block the dopamine transporter as one mechanism of action for achieving their therapeutic effects (Spencer et al 2000). In mice, eliminating SLC6A3 gene function leads to two features suggestive of ADHD: hyperactivity and deficits in inhibitory behavior. And like ADHD children, treating these "knockout" mice with stimulants reduces their hyperactivity (Gainetdinov et al 1999b; Giros et al 1996). Similar findings were seen when SLC6A3 activity was reduced to 10% of normal (Zhuang et al 2001).

The SLC6A3 knockout mouse model shows the potential complexities of gene–disease associations. The loss of the SLC6A3 gene has many biological effects: initially, these mice show increased extracellular dopamine, a doubling of the rate of dopamine synthesis (Gainetdinov et al 1998), decreased dopa-

mine and tyrosine hydroxylase in the striatum (Jaber et al 1999), and a nearly complete loss of functioning of dopamine autoreceptors (Jones et al 1999). Eventually, feedback mechanisms reduce the output of dopamine from striatal neurons, leading to a hypodopaminergic state (Gainetdinov et al 1999a). Bezard et al (1999) showed that mice without SLC6A3 function did not experience neurotoxin-induced dopaminergic cell death, and another study found a gradient effect such that mice with zero, one, and two functional SLC6A3 genes showed increasing susceptibility to neurotoxins (Gainetdinov et al 1997). These studies suggest that individual differences in SLC6A3 might mediate susceptibility to neurotoxins having an affinity for the dopamine transporter.

In ADHD adults, Dougherty et al (1999) measured striatal dopamine transporter activity by single photon emission computed tomography with the radiopharmaceutical iodine-123-labeled Altropane. They found dopamine transporter activity to be elevated by approximately 70% in ADHD adults. This finding was replicated by Krause et al (2000) with a different ligand (TRODAT-1). After treatment with methylphenidate, ligand-binding to the dopamine transporter was reduced to normal levels. In contrast, van Dyck et al (2002) did not find altered dopamine transporter levels, possibly owing to use of a different ligand, Iodine-123-beta-CIT.

Using a family-based association study, Cook et al (1995) first reported an association between ADHD and the 10-repeat allele of a tandem repeat polymorphism located in the 3′ untranslated region of SLC6A3. A meta-analysis by Curran et al (2001) of nine independent samples from 664 informative heterozygous parental transmissions found a small positive but nonsignificant OR (1.16). These investigators found evidence for significant heterogeneity among data sets. Several of the original studies included in the meta-analysis presented stronger findings when all data (not just data from complete trios) were considered (Daly et al 1999; Waldman et al 1998). One study (Barr et al 2001c) examined a haplotype between the 10-repeat allele and SNPs in intron 9 and exon 9 that were in strong linkage disequilibrium and found a haplotype significantly associated with ADHD. In a meta-analysis of 11 family-based samples (9 of which overlap with the Curran et al [2001] meta-analysis), Maher et al (2002) reported a nonsignificant OR of 1.27.

Since the publication of the two meta-analyses, several additional studies have appeared in the literature. Todd et al (2001a) reported on a large family-based twin sample, finding no association with the 10-repeat allele for either the categoric DSM-IV ADHD diagnosis, subtypes, or a series of eight latent classes based on ADHD symptoms. In a sample of 110 Taiwanese families, Chen et al (2003) found an association with the 10-repeat allele (OR = 2.9). Payton et al (2001b) stratified pairs of identical twins on the DuPaul rating scale and compared concordant high scorers (n = 50) with low scorers (n = 42) and found a nonsignificant trend for increased frequency of the 10-repeat allele among high scorers. One case–control study found essentially equal allele frequencies in the cases and control subjcts (Smith EA et al 2003). Two other studies examined quantitative traits, rather than the presence or absence of ADHD, for association with SLC6A3. One group reported an association with increasing symptom severity as assessed by a DSM-IV criteria checklist (Waldman et al 1998). Muglia et al (2002a) tested for association between SLC6A3 alleles and ADHD using quantitative data derived from two rating scales, but no association was detected when ADHD was considered as a continuous trait.

When results from the family-based studies noted above are pooled, the OR is small (1.13; 95% CI 1.03-1.24) but significant, suggesting that the dopamine transporter gene merits further investigation but that its effect is modest.

Dopamine Beta-Hydroxylase. Dopamine beta-hydroxylase (DBH) is the primary enzyme responsible for conversion of dopamine to norepinephrine. In their Tourette's syndrome sample, Comings et al (1996b) examined a Taq1 restriction site polymorphism in intron 5 and found a significant association with ADHD symptom scores. Smith and colleagues (Smith KM et al 2003) reported a case–control analysis of two DBH polymorphisms: the TaqI A polymorphism (intron 5) and a GT repeat polymorphism located approximately 4.5 kb upstream of the transcription start site; the latter allele had previously been associated with DBH serum levels (Cubells et al 1998). In their sample of 105 ADHD cases and 68 community control subjects, logistic regression analysis indicated a significant association between the A1 allele of the Taq 1 polymorphism and ADHD (OR = 1.96; 95% CI 1.01–3.79). For the GT repeat polymorphism, the A4 allele was nonsignificantly more common among cases than control subjects.

In addition to these case–control studies, several family-based association analyses of DBH have been reported. Daly et al (1999) studied the Taq1 polymorphism in an Irish sample of 86 trios and 19 parent–child pairs. They found a significant association between the A2 allele and ADHD (RR = 1.31) that was largely attributable to cases in which there was a parental history of ADHD. Further analyses suggested the association was strongest for the combined subtype of ADHD. Roman et al (2002) found further support for this association in a sample of 88 Brazilian families. In their study, the A2 allele was associated with ADHD, especially with the combined subtype. In contrast to Daly et al, however, excess transmission of the A2 allele was more common among families without a parental history of ADHD.

In a Canadian study of 117 families with children with ADHD, Wigg et al (2002) reported a nonsignificant excess transmission of the A2 allele. They also observed no evidence of linkage or association for the dinucleotide repeat polymorphism and an insertion/deletion polymorphism in the region 5′ to the transcription start site (both of which had been associated with serum DBH levels). Analysis of haplotypes of these three polymorphisms was also negative. In a family-based analysis of 104 trios from the United Kingdom, Payton et al (2001a) examined a G/T SNP in exon 5 of DBH and found no evidence of association. The dinucleotide repeat polymorphism was also studied by Hawi et al (2003) in the Irish sample in which the Taq1 association was previously observed. They also examined an EcoN1 restriction site polymorphism in exon 2 and an MspI polymorphism in intron 9. There was no evidence of association for these additional polymorphisms. A two-marker haplotype comprising allele 1 of the exon 2 polymorphism and A2 of the Taq1 polymorphism was preferentially transmitted to ADHD cases. Despite the mixed evidence for association between DBH and ADHD, when the family-based studies are pooled, they jointly suggest a significant association between ADHD and the 5′ Taq1 polymorphism (OR = 1.33; 95% CI 1.11-1.59).

Tyrosine Hydroxylase. Tyrosine hydroxylase (TH) catalyzes the conversion of tyrosine to dihydroxy-phenylalanine and thus plays a role in the synthesis of dopamine. Thus far, only three studies have examined the association between polymorphisms in the TH gene and ADHD. All have been negative. Barr et al (2000b) found no association between ADHD and a tetranucle-

otide repeat in intron 1 in a sample of 72 trios plus 10 one-parent families and 15 affected siblings. Payton et al (2001a) found no association with the same polymorphism and 105 triads. Finally, in a case–control study, Comings et al (1995) found no association between this polymorphism and ADHD in a sample of 74 cases and 89 control subjects.

Catechol-O-Methyltransferase. Catechol-O-methyltransferase (COMT) catalyzes a major step in the degradation of dopamine, norepinephrine, and epinephrine. Seven family-based studies examined the Val108Met polymorphism in the COMT gene, which yields either a high- or low-active form of COMT (Syvanen et al 1997). Five of these found no significant association (Barr et al 1999; Hawi et al 2000; Manor et al 2000; Payton et al 2001a; Tahir et al 2000a). Two studies reported statistically significant associations, though one (Eisenberg et al 1999) study of 48 children subsequently corrected their report to include less over-transmission of the Val allele than originally reported (revised $p = .048$), and the other (Qian et al 2003b), the only one of these to examine Chinese rather than Caucasian ADHD cases, was significant only when limited to male cases. Our pooled analysis of these studies showed no evidence of association between ADHD and COMT (OR = 1.0, p = ns).

Monoamine Oxidase A. The monoamine oxidase A (MAO-A) enzyme moderates levels of norepinephrine, dopamine, and serotonin in the central nervous system, and MAO-A knockout mice display numerous abnormalities in these neurotransmitter systems (Cases et al 1998). A case–control study of the X-linked MAO-A gene reported an association between a 30-bp tandem repeat in the promoter region and ADHD in 110 male and 19 female Israeli ADHD cases compared with control subjects, with a particularly large effect noted in the small (n = 19) subset of female cases (Manor et al 2002b). That study also found an association between the risk polymorphism and errors of commission on a neuropsychological test of attention.

The promoter-region repeat was also significantly associated with ADHD in a sample of 133 Israeli families (Manor et al 2002b) but not in a similarly-sized family-based study by Lawson et al (2003). Among 82 Chinese families, a dinucleotide tandem repeat polymorphism was associated with ADHD (Jiang et al 2001), though a study in a Caucasian cohort failed to replicate this association (Payton et al 2001a).

The Noradrenergic System

Noradrenergic Receptors: ADRA2A, 2C, and 1C. Three adrenergic receptors have been examined in ADHD. The α-2A adrenergic receptor (ADRA2A) has a promoter-region SNP (C→G, −1291) that has been examined in both case–control and family-based analyses. In their sample of patients with Tourette's syndrome, Comings et al (1999) reported an association between genotypes at this SNP and ADHD symptom scores. A subsequent analysis of the sample (Comings et al 2003), which examined a broad range of psychiatric symptoms, concluded that the G allele was associated with ADHD and oppositional defiant or conduct disorder symptoms, whereas the C allele was associated with a spectrum of other conditions, including panic attacks, obsessive compulsive disorder, addictions, and affective and schizoid symptoms. In contrast to these positive findings in ADHD patients with Tourette's syndrome, two family-based studies failed to detect association between ADRA2A and the diagnosis of ADHD (Roman et al 2003; Xu et al 2001), but one of these found a significant association of the G allele with elevated inattentive and combined symptom scores (Roman et al 2003).

A dinucleotide repeat polymorphism located approximately 6 kb from the gene that codes for the α-2C adrenergic receptor (ADRA2C) has also been examined in both case–control and family-based analyses. Comings et al (1999), in their sample of Tourette's syndrome cases and control subjects, found an association between this polymorphism and ADHD symptom scores, but it was not significant after Bonferroni correction. Two subsequent family-based analyses, one in 103 families and another in 128 families, showed no evidence of association (Barr et al 2001b; De Luca et al 2004b). The former study also examined a C-to-T SNP in codon 492 of the 1C receptor (ADRA1C) that changes cysteine to arginine but found no evidence of linkage (Barr et al 2001b).

In summary, studies of these three adrenergic receptor genes in ADHD do not suggest an association. But because studies to date have been limited by small sample sizes and examination of single polymorphisms, further investigation might be warranted.

The Norepinephrine Transporter. The norepinephrine transporter (SLC6A2) has been examined in ADHD because drugs that block the norepinephrine transporter are efficacious in treating ADHD (Biederman and Spencer 2000). In their sample of patients with Tourette's syndrome, Comings et al (2000b) found evidence for association of an SNP in SLC6A2 with ADHD symptoms. Subsequently, Barr et al (2002) examined three SNPs in SLC6A2 (one in exon 9, intron 9, and intron 13, respectively) in 122 ADHD families and found no evidence of association for these loci or haplotypes comprising them. No association with intron 7 and intron 9 SNPs was seen in a study of Irish families (McEvoy et al 2002) or with a restriction fragment length polymorphism in a set of families with adult ADHD offspring (De Luca et al 2004a).

The Serotonergic System

Serotonin Receptors: HTR1B and HTR2A. Two family-based association studies examined a silent SNP (G861C) in the gene coding for the serotonin HTR1B receptor. In predominantly Caucasian samples, both studies found over-transmission of the G allele, though this finding only reached statistical significance in the very large study by Hawi et al (2002), which reported pooled results from four sites. When Quist et al (2003) analyzed paternal transmission, their association reached significance as well. The pooled OR for the G861C SNP is 1.44 (95% CI 1.14–1.83).

The serotonin HTR2A receptor gene has been examined in two case–control studies. Zoroglu et al (2002) found no associations between the T102C and G1438A polymorphisms and ADHD. Conversely, in a sample of women with seasonal affective disorder, Levitan et al (2002) found an association between the number of C alleles and greater scores on a self-report measure of childhood ADHD. A second coding polymorphism in the HTR2A receptor gene (His452Tyr) was associated with ADHD in one family study (Quist et al 2000) but not in another, much larger study (Hawi et al 2002). Of note, the latter study found an association with the His allele when families of Irish origin were analyzed alone. The former study also noted no association between the T102C polymorphism and ADHD. The pooled OR for all HTR2A studies is 1.1 and is not statistically significant.

Overall, preliminary findings suggest an association between the HTR1B gene and ADHD, which merits further investigation. Evidence is less consistent for the HTR2A gene but largely negative thus far.

Serotonin Transporter. The serotonin transporter gene (5-HTT; SLC6A4) is perhaps the best-studied gene in psychiatric

genetics, with associations reported for a broad range of diagnoses and traits (Anguelova et al 2003a, 2003b) Four case–control studies reported an association between a 44-bp insertion/deletion polymorphism (5-HTTLPR) in the promoter region of SLC6A4 and a diagnosis of ADHD (Seeger et al 2001). Among 80 children with hyperkinetic disorder with or without conduct disorder, compared with control subjects, the "long" allele was over-represented. Two subsequent studies found similar result. Retz et al (2002), in contrast to other studies, examined a continuous measure of ADHD symptoms. Zoroglu et al (2002) also examined a variable number of tandem repeats (VNTR) polymorphism (STin2) and found a significant association with ADHD. A small study of aggressive children also noted an association between the long allele of 5-HTTLPR, though not the VNTR, and ADHD (Beitchman et al 2003).

Similarly, two family studies reported over-transmission of the long allele of 5-HTTLPR, consistent with case–control findings, though neither reached statistical significance. In their sample of 98 trios, Manor et al (2001) found a significant association with combined-type ADHD. Kent et al (2002) examined two other polymorphisms (an SNP in the 3′ untranslated region and a tandem repeat) and identified significant associations for the SNP and for a haplotype including this SNP and 5-HTTLPR. Another study, which examined behavioral measures in 87 adopted children, found no association with the 5-HTTLPR overall, but in a regression model including an interactive effect with parental alcohol abuse, did identify a significant association (Cadoret et al 2003). When the 5-HTTLPR studies are combined, the pooled OR for the long allele is 1.31 (95% CI 1.09–1.59).

Tryptophan Hydroxylase. Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the synthesis of serotonin, and TPH polymorphisms have been associated with aggression and impulsivity (Manuck et al 1999). Two family-based studies examined the TPH gene in ADHD. One study of 69 Han Chinese trios found no association with an SNP (A218C) in intron 7 (Tang et al 2001). A second study examined two SNPs among more than 350 Han Chinese youth with ADHD with and without learning disability and their families (Li et al 2003). Although neither SNP showed biased transmission individually, a haplotype composed of the 218A and 6526G alleles seemed to be under-transmitted, particularly for ADHD youth with learning disabilities. Thus, further study of TPH might be warranted.

Other Candidate Genes

Acetylcholine Receptors: CHRNA4 and CHRNA7. The nicotinic acetylcholine receptors are ligand-gated ion channels composed of five subunits, one of which is the α-4 subunit (CHRNA4), which has been examined in several studies in ADHD. In a case–control analysis of ADHD symptom scores among cases with a primary diagnosis of Tourette's syndrome, Comings et al (2000a) found evidence of association with an intron 1 dinucleotide repeat polymorphism of the CHRNA4 gene. Two family-based analyses of the gene provide conflicting evidence. Kent et al (2001) found no significant evidence of association with a Cfo1 restriction site polymorphism in exon 5 in a study of 68 trios; however, a larger study of families ascertained from a twin sample did find association between ADHD symptoms and CHRNA4 polymorphisms. Todd et al (2003) examined seven SNPs encompassing exons 2 and 5, as well as haplotypes of these markers. In addition to examining the phenotype of DSM-IV ADHD, they used latent class analysis to derive two phenotypic subtypes of ADHD symptoms: severe inattentive and severe combined. Haplotype analysis indicated association between haplotypes of markers, including exon 2 and haplotypes of exon 2 and 5 markers with DSM-IV ADHD, the DSM-IV inattentive subtype, and the latent class inattentive subtype. After correction for multiple comparisons, further analysis of the SNPs in and around exon 2 revealed significant association only for latent class inattentive ADHD with an intronic SNP (G/A) near the exon/intron boundary at the 3′ end of exon 2. The G allele was over-transmitted, although this finding is based on only 20 informative transmissions.

In a family-based study of 206 trios, Kent et al (2001) examined the gene that codes for the α-7 subunit of the nicotinic acetylcholine receptor family (CHRNA7). They did not find an association between ADHD and any of three repeat polymorphisms close to the gene.

Glutamate Receptors. Two family-based studies have examined the GRIN2A gene, which codes a subunit of the *N*-methyl-D-aspartate (NMDA) receptor. Glutamate and the NMDA receptor have been implicated in cognition in both animal and human studies; the GRIN2A gene is an appealing positional candidate gene as well, located under a linkage peak at 16p13, previously associated with ADHD (Smalley et al 2002). In a family-based analysis of 238 families, an SNP in exon 5 was significantly associated with ADHD ($\chi^2 = 3.7$, $p = .04$); haplotypes including additional SNPs were more weakly associated (Turic et al 2004). Among 183 families, however, no evidence for association was identified for this SNP ($\chi^2 = .11$, $p = .74$) or three others (Adams et al 2004).

Synaptosomal-Associated Protein 25. Several investigators have used the coloboma mouse model to investigate the genetics of ADHD. 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, deficits in hippocampal physiology, which might contribute to learning deficiencies, and deficits in Ca2+-dependent dopamine release in dorsal striatum (Wilson 2000).

The coloboma deletion region includes the gene encoding synaptosomal-associated protein 25 (SNAP-25), a neuron-specific protein implicated in exocytotic neurotransmitter release. Hess et al (1992) suggested that interference with SNAP-25 might mediate the mouse's hyperactivity. As predicted by this hypothesis, when these investigators bred a SNAP-25 transgene into coloboma mice, their hyperactivity was reduced. Moreover, other work suggested that reduced SNAP-25 expression leads to striatal dopamine and serotonin deficiencies, which might be involved in hyperactivity (Raber et al 1997). Treatment with amphetamine (but not methylphenidate) reverses the mouse hyperactivity (Wilson 2000). This latter finding is consistent with the mechanism of action of these two stimulant drugs. Both treat ADHD symptoms by blocking the dopamine transporter, but only amphetamine cases reverse transport of dopamine through the dopamine transporter, an effect that could compensate for the reduced exocytotic dopamine release that might be a consequence of the SNAP-25 mutation.

Hess et al (1995) tested the idea that the human homolog of the mouse coloboma gene could be responsible for ADHD by completing linkage studies of ADHD families, using markers on human chromosome 20p11–p12, which is syntenic to the coloboma deletion region. They used five families for which segregation analysis suggested that ADHD was due to a sex-influenced, single gene. But no significant linkage was detected between ADHD and markers on chromosome 20p11–p12.

Four family-based studies of SNAP-25 examined two biallelic

Table 1. Significant Pooled Odds Ratios for Gene Variants Examined in Three or More Case–Control or Family-Based Studies[a]

Gene	Study Design	Pooled OR	95% CI
Dopamine D4 Receptor (exon III VNTR, 7-repeat)	Family	1.16	1.03–1.31
Dopamine D4 Receptor (exon III VNTR, 7-repeat)	Case–control	1.45	1.27–1.65
Dopamine D5 Receptor (CA repeat, 148 bp)	Family	1.24[a]	1.12–1.38
Dopamine Transporter (VNTR, 10-repeat)	Family	1.13	1.03–1.24
Dopamine β-Hydroxylase (TaqI A)	Case–control	1.33	1.11–1.59
SNAP-25 (T1065G)	Family	1.19	1.03–1.38
Serotonin Transporter (5-HTTLPR long)	Case–control	1.31	1.09–1.59
HTR1B (G861C)	Family	1.44	1.14–1.83

OR, odds ratio; CI, confidence interval; VNTR, variable number of tandem repeats.
[a]Lowe et al 2004.

SNPs (T1069C and T1065G) separated by 4 bp at the 3′ end of the gene (Barr et al 2000a; Brophy et al 2002; Kustanovich et al 2003b; Mill et al 2004b). Barr et al (2000a) initially reported a modest association of a haplotype formed by these two adjacent SNPs. In the largest study of these SNPs, Kustanovich et al (2003b) did not detect an association to these SNPs but noted a slight predominance of paternal over-transmission of the haplotype implicated by Barr et al. But this finding was not supported by Brophy et al (2002). Two of these studies, which seem to examine overlapping samples, investigated a microsatellite in intron 1, again with marginal evidence for an association (Mill et al 2002, 2004b). In another study from the same group, eight polymorphisms were investigated (two microsatellites and six SNPs) (Mill et al 2004b). Three individual markers (SNP -2015 A/T located in the putative promoter region, a microsatellite in intron 1, and 80609 G/A located in intron 7), were associated with ADHD. Using a sliding window approach to investigating the haplotypes, the investigators examined sets of three marker haplotypes and detected stronger evidence for association than for individual markers. Each of the SNAP-25 candidate gene studies tested the same two adjacent SNPs, and there is little agreement between them as to whether there is an association and which allele is associated. Despite these conflicting results, the pooled analyses for T1065G shows significant evidence for an association with ADHD (OR = 1.19; 95% CI 1.03–1.38).

Discussion

Although twin studies demonstrate that ADHD is a highly heritable condition, molecular genetic studies suggest that the genetic architecture of ADHD is complex. The handful of genome-wide scans that have been conducted thus far show divergent findings and are, therefore, not conclusive. In contrast, the many candidate gene studies of ADHD have produced substantial evidence implicating several genes in the etiology of the disorder. As Table 1 shows, for the eight genes for which the same variant has been studied in three or more case–control or family-based studies, seven show significant evidence of association with ADHD on the basis of the pooled OR: DRD4, DRD5, DAT, DBH, 5-HTT, HTR1B, and SNAP-25.

The ORs for these associations range from 1.18 to 1.46. These small ORs are consistent with the idea that the genetic vulnerability to ADHD is mediated by many genes of small effect. Moreover, they suggest one explanation for the frequent failure to replicate initial reports of association: many individual studies might be underpowered to find significant associations if the effects are modest (Ioannidis et al 2001; Lohmueller et al 2003). Several other factors mighty contribute to inconsistent results. For example, studies in which case–control designs are used are also vulnerable to identifying spurious associations because of population admixture, a limitation not present in family-based studies (Devlin et al 2001). Other studies examined different ethnic groups, in which allele frequencies might differ, or used different methods of ascertainment or phenotyping.

These small and sometimes inconsistent effects emphasize the need for future candidate gene studies to implement strategies that will provide enough statistical power to detect such small effects. Such strategies, which have already been used for some ADHD candidate genes, include meta-analyses, collaborative studies with large sample sizes, or examination of refined phenotypes that might reduce heterogeneity. Such refined phenotypes might be defined by examining disease subtypes defined by symptoms (Curran et al 2003), illness persistence (Faraone et al 2000b), or concurrent psychiatric diagnoses, such as bipolar disorder (Faraone et al 1997b, 2001a; Wozniak et al 1995) or conduct disorder (Faraone 2001; Faraone et al 1991, 1997a). The use of measurements of neuropsychiatric function or brain imaging might also aid in phenotypic refinement, as it has been applied in schizophrenia, for example (Egan et al 2001). Additionally, rather than examining a single polymorphism, strategies that examine groups of polymorphisms spanning haplotype blocks should provide a more complete assessment of candidate genes. Finally, ecogenetic studies of gene–gene interactions and gene–environment interactions have yielded important leads in other psychiatric diagnoses, such as major depressive disorder (see, e.g., Caspi et al 2003), and will likely be necessary to further clarify the mechanisms by which risk genes interact with each other and with nongenetic factors to yield the behavioral phenotype of ADHD.

This work was supported by National Institute of Health grants R01HD37694, R01HD37999, and R01MH66877 to SVF, K23MH67060 to RHP, and K08MH66072 to AED.

Aspects of this work were presented at the conference, "Advancing the Neuroscience of ADHD," February 28, 2004 in Boston, Massachusetts. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant from McNeil Consumer & Specialty Pharmaceuticals.

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