Molecular Genetics of Attention Deficit Hyperactivity Disorder

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Attention deficit/hyperactivity disorder (ADHD) is among the most common childhood-onset psychiatric disorders. The worldwide prevalence of ADHD in children is 8% to 12%,[1] and estimated to be 4% in adults in the United States by the National Comorbidity Survey.[2] Early studies found the risk for ADHD among parents of children who had ADHD to be increased by between two- and eightfold, with similarly elevated risk among siblings.[3] Faraone and colleagues[4] extended these findings to families ascertained through adult probands meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for either full ADHD or late-onset ADHD.

However, adoption and twin studies are necessary to disentangle genetic from environmental sources of transmission observed in family studies. Three studies found that biologic relatives of ADHD[5] or hyperactive children[6,7] were more likely to have hyperactivity than adoptive relatives. A more direct method of examining the heritability of ADHD is to study twins. The extent to which monozygotic twins are more concordant for ADHD than dizygotic twins can be used to compute the degree to which variability in ADHD in the population can be accounted for by genes (ie, heritability). Faraone and colleagues[8] reviewed 20 twin studies from the United States, Australia, Scandinavia, and the European Union and reported a mean heritability estimate of 76%, showing that ADHD is among the most heritable of psychiatric disorders.

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GENETIC LINKAGE STUDIES

To find regions of chromosomes that might harbor genes for ADHD, several groups have conducted genome-wide linkage scans.[9–14] This approach examines many DNA markers across the genome to determine if any chromosomal regions are shared more often than expected among family members who have ADHD.

A study of 126 American affected sibling pairs found four regions that showed some evidence of linkage (LOD scores >1.5): 5p12, 10q26, 12q23, and 16p13.[9] An expanded sample of 203 families found stronger evidence for the 16p13 region, previously implicated in autism, with a maximum LOD score of 4.[10] A study of 164 Dutch affected sibling pairs also identified a peak previously noted in autism, at 15q15, with a peak LOD score of 3.5.[11] 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 Columbia implicated 8q12, 11q23, 4q13, 17p11, 12q23, and 8p23.[12] Pooled analyses[10,11] suggest that the genetic background in the differing populations is distinct and that the lack of consistent findings is a reflection of this between-population heterogeneity,[13] but did identify an area of linkage in these pooled analyses (5p13) that may reflect a common risk locus.

A study of 155 sibling pairs from Germany reported a maximum LOD score of 2.59 for chromosome 5p at 17cM. They also reported nominal evidence for linkage to chromosomes 6q, 7p, 9q, 11q, 12q, and 17p, which had also been identified in previous scans.[14] Faraone and colleagues[15] found no regions of significant or suggestive linkage in an affected sibling pair linkage analysis on 217 families with 601 siblings diagnosed with ADHD.

Although some overlap is present in nominally significant linkage peaks, no evidence exists for the replication of a genome-wide significant finding using strict criteria.[16] To determine if any common linkage signals were present among these studies, Zhou and colleagues[17] conducted a Genome Scan Meta Analysis of these data. They reported genome-wide significant linkage ($P_{Statistical\ Ratio} = .00034$; $P_{Odds\ Ratio} = .04$) for a region on chromosome 16 between 64 Mb and 83 Mb. Although this finding is intriguing and worthy of follow-up, the lack of significant findings for other loci suggests that many genes of moderately large effect are unlikely to exist and that the method of association will be more fruitful in the search for ADHD susceptibility genes.

Genetic Association Studies

In contrast to the scarcity of linkage studies, many candidate gene association studies have been conducted. Several meta-analyses suggest strong association with ADHD and the dopamine D4 receptor gene (DRD4, 48-bp VNTR),[18,19] the dopamine D5 receptor gene (DRD5, 148-bp microsatellite marker),[18,20] the dopamine β-hydroxylase gene (DBH, 5′ taq1 A allele),[8] the synaptosomal-associated protein 25 gene (SNAP-25, T1065G single-nucleotide polymorphism [SNP]),[8] the serotonin transporter gene (SLC6A4, 44-bp insertion/deletion in the promoter region [5-HTTLPR]),[8] and the serotonin 1B receptor gene (HTR1B, G861C SNP).[8] Meta-analysis has also suggested a weak association with ADHD and the dopamine transporter gene (SLC6A3, 480-bp VNTR in the 3′ untranslated region [UTR]),[18,21,22] but no association with the catechol-O-methyltransferase gene (COMT, Val108Met polymorphism).[23]

A major advance in the molecular genetics of ADHD was the publication of the International Multisite ADHD Gene (IMAGE) project in which 51 genes were analyzed for association with ADHD. Families were recruited through an ADHD combined-type child proband (N = 674) who had at least one full sibling (n = 808) and one biologic parent (N = 1227 parents) available for study. A high density SNP map was

constructed for genes involved in the regulation of neurotransmitter pathways implicated in ADHD (dopamine, norepinephrine, and serotonin) based on tagging SNPs and SNPs within known functional regions. This study is the most in-depth genetic association study performed in the largest set of ADHD patients to date and found evidence of association with ADHD and 18 genes.

Taken together this literature strongly suggests a contribution of genetic factors in the etiology of ADHD. In this review, we provide an update on the progress of molecular genetic studies published since the completion of these meta-analyses. Results from the IMAGE project will be discussed separately for each gene.

ASSOCIATION STUDIES OF CATECHOLAMINERGIC GENES
The Dopamine D4 Receptor (DRD4)

Both noradrenaline and dopamine are potent agonists of DRD4,[24] and the D4 receptor is prevalent in frontal-subcortical networks implicated in the pathophysiology of ADHD by neuroimaging and neuropsychological studies.[25] 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.[26,27] Faraone and colleagues[8] conducted a meta analysis of the 7-repeat allele of the exon III polymorphism and found statistically significant association with ADHD in both case-control (odds ratio = 1.45 (95% CI 1.27–1.65)) and family based OR = 1.16 (95% CI 1.03–1.31) studies. Li and colleagues[18] reported a pooled OR of 1.34 (1.23–1.45) in 33 studies.

Not included in these meta-analyses of the exon III DRD4 48-bp VNTR were a prospective follow-up study of German children in which the 7-repeat DRD4 allele was associated with increased incidence and persistence of ADHD in boys up to 11 years of age,[28] a positive association with the 6 and 7 repeat alleles in a sample of 44 Indian ADHD trios (RR = 1.81; P = .03),[29] and a negative association in 126 Korean ADHD families (P = .67).[30] Carrasco and colleagues[31] also failed to document an association with the 7 repeat allele in a small case-control study of 26 Chilean children with ADHD, but found a significant interaction with this DRD4 marker and the dopamine transporter gene suggesting that children with the risk alleles at both loci are at greater risk of ADHD. In the large and comprehensive IMAGE project, the association with this VNTR and ADHD was not statistically significant (P<.09) but the odds ratio (1.18) was very close to that observed in meta-analyses.

A small number of studies have assessed other DRD4 polymorphisms; however, these data have not been conclusive. McCracken and colleagues[32,33] found an association between ADHD and a 5′ 120-bp repeat 1.2 kb upstream of the initiation codon. However, Barr and colleagues,[34] Todd and colleagues,[35] Brookes and colleagues,[36] and Bhaduri and colleagues[37] found no association between ADHD and this marker. Significant evidence of association was found by Arcos-Burgos and colleagues,[12] but only with the 5′ 120-bp marker included with the exon III 48-bp 7-repeat allele in haplotype analysis.

Barr and colleagues[34] found no association between ADHD and two SNPs in the promoter region (rs747302 and rs1800955), but Lowe and colleagues[38] observed a significant over transmission of the rs1800955-A allele and a trend toward association with the rs747302-C allele. Brookes and colleagues[39] did not genotype these SNPS in the IMAGE project, but observed nominal association with a SNP (rs9195457) for which the LD structure with previously associated SNPs could not be determined.

Although it has been suggested that the DRD4 gene may be particularly relevant to symptoms of inattention, the literature suggests that this may not be so. Rowe and

colleagues[40] found that fathers of ADHD children with the 7-repeat allele had higher levels of retrospectively reported inattention symptoms, and Levitan and colleagues[41] found an association between this allele and greater self-reported childhood inattention in women with seasonal affective disorder. However, Todd and colleagues[42] found no association with the exon III 48-bp VNTR and any ADHD symptom profiles or DSM-IV subtypes in pooled analysis of 2,090 children. Similarly, Mill and colleagues[43] found no association with the 7-repeat allele and a quantitative measure of ADHD symptom profiles in 329 pairs of male twins ascertained in England and Wales. Although the 7-repeat allele was not present in a sample of Korean ADHD children, Kim and colleagues[30] reported no variation of inattentive symptoms with the number of repeats but rather observed a greater severity of hyperactive/impulsive symptoms in subjects with a 5-repeat allele.

Furthermore, on neuropsychological measures of attention, subjects possessing the 7-repeat allele have demonstrated significantly better attention than subjects with fewer repeats[44–46] or demonstrated no difference on similar measures of attention.[47] However, Bellgrove and colleagues[46] found that the rs747302-A allele was associated with sustained attention deficits while the 7-repeat allele of the exon III VNTR was associated with improved performance. Thus, they conclude that such risk alleles have dissociable effects on cognition in ADHD children.[46]

Two studies have provided evidence documenting strength of a DRD4-ADHD relationship relative to other phenotypes hypothesized to also be associated with DRD4: autism[48] and a novelty seeking temperament.[49] Grady and colleagues[48] found no evidence of an over-representation of rare DRD4 variants in a sample of children with autism relative to geographically matched controls, while a sample of ADHD children had a fourfold increase in novel alleles compare with geographically matched controls. Furthermore, Lynn and colleagues[49] examined the relationship between ADHD, novelty seeking and the exon III DRD4 48-bp VNTR and found independent associations with ADHD/novelty seeking, and ADHD/DRD4, but not with DRD4/novelty seeking. Although not conclusive these studies suggest that the association between ADHD and DRD4 is relatively specific (ie, relative to autism) and not confounded by common comorbid behaviors (ie, increased novelty seeking).

The Dopamine 5 Receptor (DRD5)

The most widely studied polymorphism for DRD5 has been a dinucleotide repeat that maps approximately 18.5 kb 5′ to the transcription start site.[50] Meta-analysis of 14 independent family-based studies suggested a significant association of the 148-bp allele with ADHD (OR = 1.2; 95% CI 1.1–1.4)[20] that was confirmed in updated analyses conducted by Li and colleagues[18] (OR = 1.3; 95% CI 1.2–1.5). Not included in these meta-analyses is a study by Mill and colleagues[43] examining quantitative measures of ADHD symptoms in 329 pairs of male twins ascertained in England and Wales. Again, the 148-bp allele was statistically significantly associated with ADHD, but unfortunately the direction of effect was in the opposite direction: the risk allele was associated with lower hyperactivity scores.[43]

Other markers within DRD5 have also been found to be associated with ADHD. Hawi and colleagues[50] studied two additional 5′ microsatellite markers and a SNP in the 3′ UTR. The 3′ SNP was associated with ADHD (relative risk = 1.6) and haplotype analyses showed an association with ADHD and a two-marker haplotype of one of the 5′ microsatellite markers (D4S1582) and the dinucleotide repeat (DRD5-PCR1) (P = .000107), a two-marker haplotype comprising DRD5-PCR1 and the 3′ SNP (P = .0099), and a haplotype comprised of all three of these markers (P = .0013).

The Dopamine Transporter Gene (DAT, SLC6A3)

There are several reasons that SLC6A3 has been considered a suitable candidate for ADHD. Stimulant medications, which are efficacious in treating ADHD, block the dopamine transporter as one mechanism of action for achieving their therapeutic effects.[51] In mice, eliminating SLC6A3 gene function leads to two features suggestive of ADHD: hyperactivity and deficits in inhibitory behavior. Treating these "knockout" mice with stimulants reduces their hyperactivity.[52,53]

Using a family-based association study, Cook and colleagues[54] first reported an association between ADHD and the 10-repeat allele of the 3′UTR VNTR. Our previous meta-analysis of family-based studies resulted in a small but significant odds ratio (1.13, 95% CI 1.03–1.24), however Li and colleagues[18] updated this work and found no evidence of association with ADHD and the 10-repeat allele in family-based studies (OR = 1.04, 95% CI = 0.99–1.14), as well as considerable evidence of heterogeneity between studies (p(Q) = 0.000001). A subsequent meta-analysis of this gene found small but significant association with ADHD for family-based TDT studies (OR = 1.17, 95% CI = 1.05–1.30).[21] The odd ratio for seven family-based HHRR studies was 1.5, but it was not significant. Although there were only six case-control studies, their combined odds ratio of 0.95 would seem to disconfirm the family-based studies.[21]

Thus, the lack of consistent association with the 3′ UTR VNTR suggests that this marker itself is not directly involved in the etiology of ADHD, but it may be tagging a proximate functional polymorphism in partial linkage disequilibrium (LD) with the 10-repeat allele. In an attempt to further refine the SLC6A3 risk variant for ADHD, Brookes and colleagues[55] reported association with a haplotype comprised the 10-repeat allele in the 3′UTR and the 6-repeat allele of a 30-bp VNTR in intron 8. Of the four possible haplotype combinations of the two markers, only the 10-6 haplotype was associated with increased risk for ADHD in both populations. This finding was replicated by Brookes and colleagues[39] (OR = 1.19, P<.06) and Asherson and colleagues[56] in the second set of 383 ADHD probands from the IMAGE sample (OR = 1.27, P = .002). Bakker and colleagues[57] failed to identify an overall association with this haplotype (P = .2) or preferential over transmission of the 10-6 variant in 198 Dutch probands with ADHD.

However, evidence is emerging that environmental risk factors for ADHD might be important mediators of the risk for ADHD associated with SLC6A3. Brookes and colleagues[55] also reported a gene-environment interaction suggesting that the risk for ADHD was increased only in the presence of the 10-6 SLC6A3 haplotype when there was also exposesure to maternal alcohol use during pregnancy. Although the 9-repeat allele was significantly over transmitted in the sample[58] used by Neuman and colleagues,[59] they documented an increased risk for the severe combined ADHD profile with both SLC6A3 and the DRD4 7-repeat allele only in children who were exposed to maternal cigarette smoking during pregnancy. Similarly, Laucht and colleagues[60] found that the 3′UTR 10-repeat allele, the intron 8 6-repeat allele, and the 10-6 haplotype were associated with ADHD symptoms only in families exposed to higher psychosocial adversity.

Dopamine Beta-Hydroxylase (DBH)

DBH is the primary enzyme responsible for conversion of dopamine to norepinephrine. Comings and colleagues[61,62] examined a Taq1 restriction site polymorphism in intron 5 and found a significant association with the A1 allele and ADHD symptom scores in children with Tourette's Syndrome (TS).[62] Smith and colleagues[63] subsequently

replicated this association (OR = 1.96; 95% CI: 1.01-3.79) in ADHD subjects but Daly and colleagues[64] and Roman and colleagues[65] found over-transmission of the A2 allele. Both also found that the association was stronger in combined-type ADHD cases but Daly and colleagues[64] found that parental history of ADHD strengthened the association while Roman and colleagues[65] found stronger evidence of association in those with no parental history of ADHD. In a Canadian study of 117 families with children with ADHD, Wigg and colleagues[66] reported a non-significant excess transmission of the A2 allele. Subsequently, a case-control study of Indian ADHD children[67] and both case-control and family-based analyses of persistent ADHD cases in Canada[68] have failed to document a significant association with this marker of DBH.

Other markers of DBH have also shown a lack of significant association with ADHD. Wigg and colleagues[66] 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). A G/T SNP in exon 5 of DBH was examined in 104 trios from the UK (Payton and colleagues[69]) and in 86 trios from Ireland[50] and showed no evidence of association. Hawi and colleagues[70] also examined an EcoN1 restriction site polymorphism in exon 2 and an MspI polymorphism in intron 9 and found association for only a haplotype comprised of allele 1 of the exon 2 polymorphism and A2 of the Taq1 polymorphism. A -1021C>T polymorphism in the 5′ flanking region of DBH has been shown to account for as much as 50% of plasma DBH activity and was associated with ADHD in the Han Chinese,[71] but not in a sample of Indian ADHD children.[67] Finally, 33 SNPs were tagged for this gene in the IMAGE project, but there were no nominally significant associations with ADHD found.[39]

Monoamine Oxidase A (MAO-A)

The MAO-A enzyme moderates levels of norepinephrine, dopamine, and serotonin, and MAO-A knockout mice display numerous abnormalities in these neurotransmitter systems.[72] A case-control study of a 30-bp pair tandem repeat in the promoter region in 129 Israeli ADHD subjects suggested association with ADHD and noted a particularly large effect in the subset of female cases (n = 19).[73] The 4 and 5 repeat alleles of this promoter-region VNTR were also significantly associated with ADHD in a sample of 133 Israeli families,[73] but not in a similarly-sized family-based study by Lawson and colleagues[74] A CA-repeat microsatellite in intron 2 was associated with ADHD[75] in 82 Chinese, but this was not replicated in Caucasian samples.[69,76]

Domschke and colleagues[76] also examined a SNP in exon 8 (941G>T) and found association with the high activity G941T allele and with a haplotype containing the G941T allele, the 3-repeat allele of 30-bp VNTR and the 6-repeat of the CA microsatellite described above. Xu and colleagues[77] replicated the association with G941T allele and the over-transmission of a haplotype contain the G941T allele and the shorter 3-repeat allele of the promoter VNTR in a Taiwanese sample. Five tagged SNPs for MAO-A were statistically significantly associated with ADHD in the IMAGE sample.[39] The 941G>T SNP was not included in that analysis but the region covered by the widow of significant SNPs incorporated the location of this SNP.

The Dopamine D2 Receptor (DRD2)

The dopamine D2 receptor (DRD2) has been less extensively studied in ADHD than DRD4 and DRD5. Comings[78] compared 104 ADHD subjects (nearly all with comorbid Tourette's syndrome) to controls, and found a significant association with the TaqIA1 allele of DRD2, which they subsequently replicated.[61] This finding was replicated in

a case-control sample of Czech boys with ADHD,[79] but not in a sample of Korean alcoholics with and without ADHD.[80]

Family-based studies of DRD2 have been uniformly negative, however. Rowe and colleagues[81] 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.[82] Kirley and colleagues[83] 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. Finally, the IMAGE project examined 23 tag SNPs and found no nominally significant association with ADHD.

The Dopamine D3 Receptor (DRD3)

Barr and colleagues[84] examined a Ser9Gly exon 1 polymorphism and an intron 5 Mspl restriction site polymorphism in 100 Canadian families 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 UK family-based study of 105 families[69] and a study of 39 families of ADHD adults.[85] Comings and colleagues[86] also found no evidence for association with ADHD and comorbid Tourette Syndrome. In a sample of 146 German patients referred for forensic evaluation,[87] heterozygosity at this polymorphism was associated with higher impulsivity scores although this effect was only seen among those with a history of violence. Similarly, none of the 28 DRD3 SNPs tagged for the IMAGE project were nominally significant.[39]

Catechol-O-methyltransferase (COMT)

COMT catalyzes a major step in the degradation of dopamine, norepinephrine, and epinephrine. The most extensively studied marker for the COMT gene is the Val108Met polymorphism, which yields either a high- or low- activity form of COMT.[88] Cheuk and colleagues[23] conducted a meta-analysis of this marker and found no evidence of association with ADHD in case-control studies (OR = 0.95 [0.75–1.2], P = .7) or family-based studies using the TDT (OR = 0.95 [0.84–1.09], P = .5) or the HHRR (OR = 1.02 [0.78–1.34], P = .9). Reuter and colleagues[89] found that higher symptom scores were associated with the MET/MET genotype in German adults who were healthy or diagnosed with eating or substance use disorders and Gothelf[90] documented a 5-fold increased risk for the MET allele in 55 subjects with velocardiofacial syndrome and comorbid ADHD relative to those without comorbid ADHD. The lack of significant results from the IMAGE project[91] is consistent with the negative meta-analysis conducted by Cheuk and colleagues[23] Although these association studies rule out a simple role for the Val108Met polymorphism in the etiology of ADHD, it is of note that COMT hass been found to be highly up-regulated in a rat model of ADHD caused by prenatal exposure to polychlorinated biphenyls.[92]

Noradrenergic Receptors: ADRA2A, 2C and 1C

Three adrenergic receptors have been examined in ADHD. The alpha-2A adrenergic receptor (ADRA2A) has a promoter-region SNP (-1291 C>G) which has been examined in both case-control and family-based studies. Comings and colleagues[93] reported an association between genotypes at this SNP and ADHD symptom scores and that the G-1291C allele was associated with ADHD and oppositional defiant or conduct disorder symptoms while the C-1291G allele was associated with a spectrum of other conditions including panic attacks, obsessive compulsive disorder (OCD), addictions, affective, and schizoid symptoms.

However, family-based studies failed to detect association with -1291C>G polymorphism and the diagnosis of ADHD.[94–100] The G-1291C allele of this marker has been shown to be associated with ADHD symptom scores, but the direction of effect has been inconsistent: some studies found association with only inattentive symptoms[101] while others found association with both inattentive and hyperactive symptoms.[95,96] In contrast, Wang and colleagues[99] found no association with ADHD in a sample of Han Chinese but a trend toward lower ADHD symptom score in subjects homozygous for the G-1291C allele. Examination of other markers have been similarly inconsistent with the G-1291C allele being included in a significantly over-transmitted haplotype in a sample of 51 trios[96] while the C-1291G allele was included in a significant haplotype in sib-pair linkage study of 93 ADHD probands and 50 of their unaffected siblings.[100]

While these results suggest either a weak or no association with ADHD and the1291G>C polymorphism, they do not take heterogeneity in the presentation of ADHD into account. Schmitz and colleagues[97] conducted a unique study of exclusively inattentive-type ADHD children and found a significant association with the G-1291C allele in case-control but not family-based analyses. Waldman and colleagues[102] evaluated the moderating and mediating effects of executive function deficits on the association of ADRA2A and ADHD and found that association with ADHD was more robust in children with poorer cognitive performance. Although Stevenson and colleagues[103] reported no overall association with ADRA2A, there was a significant over-transmission of the G-1291C allele in the sub-sample with a reading disability.

A dinucleotide repeat polymorphism located approximately 6 kb from the gene which codes for the alpha-2C adrenergic receptor (ADRA2C;) has also been examined in both case control and family-based analyses. Comings and colleagues[104] found an association between this polymorphism and ADHD symptom scores, but it was not significant after Bonferroni correction. Two subsequent family-based analyses showed no evidence of association.[105,106] 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.[105] In the IMAGE project, there was no nominally significant association with any of SNPs tagged for ADRA2A or ADRA2C.[39]

The Norepinephrine Transporter (NET; SLC6A2)

SLC6A2 has been examined in ADHD because drugs that block the norepinephrine transporter are efficacious in treating ADHD.[107] Comings and colleagues[86] found evidence for association of a SNP in SLC6A2 with ADHD symptoms. Subsequently, Barr and colleagues[108] examined 3 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. Others have found no association with SNPs in intron 7 or 9[109] or with a restriction fragment length polymorphism in ADHD adults.[106] However, Xu and colleagues[110] investigated 21 SNPs spanning the NET region in 180 cases and 334 controls and reported nominally significant association with rs3785157 that was later replicated by Bobb and colleagues[111] with an additional significant association with rs998424. Although these SNPs were not found to be associated with ADHD in the IMAGE study,[39] two of the 43 tagged SNPs (rs3785143 and rs11568324) for SLC6A2 did reach nominal statistical significance. Finally, a novel promoter SNP has been shown to be possibly associated with ADHD in a set of 94 ADHD cases and 60 controls.[112]

ASSOCIATION STUDIES OF SEROTONERGIC GENES
Serotonin Receptors: HTR1B and HTR2A

Of the family-based association studies of a silent SNP (861G>C) in the gene coding for the serotonin HTR1B receptor,[111,113–116] only the multi-site study by Hawi and colleagues[113] reached statistical significance suggesting over-transmission of the G861C allele. Smoller and colleagues[115] pooled data from[113–115] and identified statistically significant over-transmission of this allele (OR = 1.35 [1.13–1.62], P = .009) that strongly suggested paternal (P = .00005) rather than maternal transmission (P = .2). There was a weak trend suggesting over-transmission of the G681 allele in Li and colleagues[117] when examining primarily inattentive ADHD subjects separately. Smoller and colleagues[115] also identified association with this ADHD subtype and a 6-SNP haplotype including the G681C allele and two promoter SNPs with functional effects on HTR1B expression. Heiser and colleagues[116] identified no association with the G681C allele but examined only the combined ADHD subtype and did not assess for paternal transmission separately. The analysis of combined-type ADHD in the IMAGE project did not identify association with any of the tag SNPs selected.[39]

The T102C, G1438A, and His452Tyr polymorphisms of the serotonin HTR2A receptor gene have also been examined for association with ADHD.[113,116,118–122] No association has been reported for the T102C and the G1438A SNPS for ADHD in.[116,119–122] Likewise Bobb and colleagues[111] found no evidence of association with ADHD and any of the SNPs of the HTR2A gene examined in either case-control or family-based analyses. However, Levitan and colleagues[123] found an association with C102T allele and greater scores on a self-report measure of childhood ADHD in a sample of women with seasonal affective disorder and Li and colleagues[121] found that the A1438G allele was associated with functional remission from ADHD in Han Chinese adolescents. A coding polymorphism in the HTR2A receptor gene (His452Tyr) was associated with ADHD in,[118,122] but not in.[113,116]

Li and colleagues[124] found significant over-transmission of the C-759T/G-697C haplotype within the HTR2C gene, but no association was observed in Bobb and colleagues[111] or in the IMAGE project.[39] Li and colleagues[125] have also reported significant under transmission of the C83097T/G83198A haplotype in the HTR4 gene, but no association with markers in HTR5A and HTR6[120] or HTR1D.[126] Genes for additional serotonin receptors (HTR1E and HTR3B) evaluated in the IMAGE project[39] have also failed to yield any significant association with ADHD.

Serotonin Transporter (HTT, SLC6A4)

A 44-base pair insertion/deletion polymorphism (HTTLPR) in the promoter region of SLC6A4 may be the most studied genetic marker in psychiatric genetics, with associations reported for a broad range of diagnoses and traits.[127,128] When the HTTLPR studies published by 2005 were combined,[8] the pooled odds ratio for the long (L) allele was 1.31 (95% CI 1.09–1.59). Curran and colleagues[129] found nominal evidence of over transmission of the L allele and strong evidence of association with a 4 SNP haplotype upstream that included the 5-HTTPR ins/del polymorphism. However, subsequent studies of this marker in 126 Korean ADHD families,[130] 197 ADHD families from the UK,[131] 196 Taiwanese ADHD familes,[131,132] 56 Indian ADHD families,[133] 209 Canadian ADHD families,[134] and 102 German ADHD families[116] have failed to identify an association with the HTTLPR. Li and colleagues[135] found statistically significant over-transmission of the S (rather than the L) allele in 279 Han Chinese ADHD families.

A 17-bp VNTR in intron 2 of SLC6A4 (STint2) was first associated with ADHD in a case-control study conducted by[119] with the 12-12 genotype being under-represented in

cases than controls. Banerjee and colleagues[133] found significant over-transmission of the 12 allele, but Heiser,[116] Xu[131] and Kim and colleagues[130] found no association and Li and colleagues[135] found evidence of under-transmission of a haplotype with the HTTLPR L allele and the STint2 12 allele. The IMAGE project found no association for the tag SNPs examined[39] and Wigg and colleagues[134] found no association with 2 functional SLC6A4 polymorphisms (rs3813034 (T/G) and Ile425Val (A/G)) and ADHD.

Tryptophan Hydroxylase (TPH and TPH-2)

TPH is the rate-limiting enzyme in the synthesis of serotonin, and TPH polymorphisms have been associated with aggression and impulsivity.[136] Two family-based studies examined the TPH gene in ADHD. One study of 69 Han Chinese trios found no association with a SNP (A218C) in intron 7.[137] A second study examined two SNPs among more than 350 Han Chinese youth with ADHD, with and without learning disability, and their families.[138,139] Although neither SNP showed biased transmission individually, a haplotype composed of the A218 and G-6526 alleles appeared to be under-transmitted (P = .03).

The gene for a second form of TPH (TPH2) located on chromosome 12q15 has also been studied. Walitza and colleagues examined two SNPs located in the transcriptional control region of TPH-2 (rs4570625 and rs11178997) a third located in intron 2 (rs4565946). Tests of the transcriptional SNPs individually and in a 2-SNP haplotype were modestly associated with ADHD in the 225 affected children (103 families), but the intron 2 SNP was not associated. Sheehan and colleagues[140] studied 8 additional SNPs in 179 ADHD families and found statistically significant evidence of association with the rs1843809-T allele (P = .0006), the rs1386497-A allele (P = .048), and a trend suggesting association with the rs1386493-C allele (P = .09). In the IMAGE project rs1843809 and rs1386497 were also significantly associated with ADHD, but the alleles implicateded in Sheehan and colleagues[140] were not.[39] Brookes and colleagues also reported an association with rs1007023 which was in perfect LD with rs1386497 from Sheehan and colleagues[39] However, Brookes and colleagues did not replicate the finding reported by Walitza and colleagues[141] and Sheehan and colleagues was not able to replicate their earlier findings in a smaller sample of 63 ADHD trios.[142]

ASSOCIATION STUDIES OF OTHER CANDIDATE GENES
Synaptosomal Associated Protein of 25kD (SNAP25)

SNAP25 is a 206 amino acid protein found on chromosome 20p12. The gene product is a presynaptic plasma membrane protein involved in the regulation of neurotransmitter release. Its relevance to ADHD was motivated by the coloboma mouse, which has a hemizygous two centimorgan deletion of a segment on chromosome 2q, including the gene encoding SNAP-25. The coloboma mutation leads to spontaneous hyperactivity, delays in achieving complex neonatal motor abilities, deficits in hippocampal physiology, which may contribute to learning deficiencies, and deficits in Ca^{2+}-dependent dopamine release in dorsal striatum.[143] Four family-based studies of SNAP25 examined two SNPs (1069T>C and 1065T>G) separated by four base pairs at the 3′ end of the gene.[144–148] Meta-analysis of these studies showed significant evidence for an association with ADHD and T1065G (OR = 1.19, 95%CI 1.03-1.38). Feng and colleagues[149] examined 12 SNPS in two independent samples of ADHD families and found significant over-transmission of the rs66039806-C, rs362549-A, rs362987-A, and the rs362998-C alleles in families from Toronto, but not California.

The IMAGE analysis of pooled data did not test these specific markers, but did demonstrate nominally statistically significant association with SNAP-25 and other markers (rs363020 and rs362567)[39] the 5′UTR. Kim and colleagues[150] examined the previously implicated SNPs and five additional SNPs (rs6077699, rs363006, rs362549, rs362987, rs362998) but found no evidence of association with ADHD in tests of individual markers or haplotypes. However, a combined TDT analysis of pooled data was modestly significant for rs3746544-T (P = .048) and rs6077690-T (P = .031). Stratification by psychiatric comorbidity further suggested that subjects with ADHD and comorbid depression may demonstrate stronger association with SNPs in SNAP-25.[150]

Acetylcholine Receptors: CHRNA4

The nicotinic acetylcholine receptors are ligand-gated ion channels composed of five subunits, one of which is the alpha-4 subunit (CHRNA4), which has been examined in several studies in ADHD. Comings and colleagues[151] found evidence of association with an intron 1 dinucleotide repeat polymorphism of the CHRNA4 gene and ADHD symptoms in a case-control study of children with Tourette Syndrome, but Kent and colleagues[152] found no significant evidence of association with a Cfo1 restriction site polymorphism in exon 5 in a study of 68 trios. Todd and colleagues[153] examined seven SNPs encompassing exons 2 and 5 as well as haplotypes of these markers and found significant association for inattentive ADHD with an intronic SNP (G/A) near the exon/intron boundary at the 3′ end of exon 2. Subsequent examination of CHRNA4 in samples of combined-type ADHD cases have not replicated this association[39,111] although the IMAGE project did report association with a SNP in the 5′ flanking region. Lee and colleagues[154] failed to replicate the association with SNPs from Todd and colleagues[153] or the IMAGE study[39] for either categorical ADHD diagnosis or symptom profile scores. In contrast to Todd and colleagues,[153] Lee and colleagues[154] found over-transmission of the rs2273505-G and rs3787141-T alleles with the combined ADHD subtype and hyperactivity–impulsivity scores.

Glutamate Receptors

The GRIN2A gene, which encodes a subunit of the N-methyl D-aspartate receptor has been examined in family-based studies of ADHD. 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.[10] In a family-based analysis of 238 families, a SNP in exon 5 (Grin2a_5) was significantly associated with ADHD (P = .01); haplotypes including additional SNPs were more weakly associated[155] However, among 183 families, no evidence for association was identified for this SNP (P = .74) or three others.[156]

Brain-derived Neurotrophic Factor (BDNF)

BDNF is a protein that supports survival of central nervous system neurons and stimulates growth and differentiation of developing neurons. A polymorphism producing an amino acid substitution (valine to methionine) at codon 66 of the BDNF may impact intracellular trafficking and activity-dependent secretion of BDNF.[157] Kent and colleagues[158] found over transmission of the Val66 allele and that this was accounted for by paternal (P = .0005) rather than maternal (P = 1.0) transmission in 341 Caucasian ADHD probands and their family members. However, Xu and colleagues[159] failed to replicate these associations with Val66 in samples from the UK or Taiwan. Xu and colleagues also examined the 270C>T SNP in the 5′-noncoding region of intron1 and

found significant over transmission of the C720T allele in Taiwanese, but not UK, ADHD families.[159] Twenty SNPs in the BDNF gene were tagged for the IMAGE project, but none were statistically significantly associated with ADHD.[39]

GENOME-WIDE ASSOCIATION STUDIES

To date, there have been two genome-wide association studies (GWAS) of ADHD. The International ADHD Genetics (IMAGE) project examined 909 trio families (two parents and one ADHD child) using 438,784 tagging SNPs designed to be in high linkage disequilibrium with all untyped SNPs in the genome. No finding achieved genome-wide significance (ie, a P-value of $<5x10^{-8}$) in the primary analysis of the ADHD diagnosis[160] but this analysis and several exploratory analyses implicated some novel genes that require further study.[161,162] Of interest, one of the exploratory analyses implicated the CDH13 gene, which was also implicated in a second GWAS of 343 ADHD adults and 250 controls.[163] CDH 13 lies under the linkage peak implicated in the meta-analysis of ADHD linkage studies discussed.

The IMAGE study also explored the existing candidate genes from the ADHD literature, to place the potential effects in context. They examined two sets of candidates. The first set comprised genes that showed significant association with ADHD in meta-analyses performed by Faraone and colleagues[8] These are SNAP25, DRD4, SLC6A3, HTR1B, SLC6A4, and DBH. The second set consisted of genes that had been nominated by the study investigators as good candidates for ADHD.[39] These were: NR4A2, PER2, SLC6A1, DRD3, SLC9A9, HES1, ADRA2C, ADRB2, ADRA1B, DRD1, HTR1E, DDC, STX1A, ADRA1A, NFIL3, ADRA2A, ADRB1, SLC18A2, TPH1, BDNF, FADS1, FADS2, ADRBK1, ARRB1, DRD2, HTR3B, TPH2, SYT1, HTR2A, SLC6A2, ARRB2, PER1, PNMT, CHRNA4, COMT, ADRBK2, CSNK1E, MAOA, MAOB, and HTR2C. Although none of the SNPs in these achieved genomewide significance, when the SNPs in these genes were analyzed as a group, the results suggested that they were weakly associated with ADHD.[160]

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. Similarly, many of the candidate genes reviewed here (ie, DBH, MAOA, SLC6A2, TPH-2, SLC6A4, CHRNA4, GRIN2A) are theoretically compelling from a neurobiological systems perspective, but available data are sparse and inconsistent. However, candidate gene studies of ADHD have produced substantial evidence implicating several genes in the etiology of the disorder. The literature published since recent meta-analyses is particularly supportive for a role of the genes coding for DRD4, DRD5, SLC6A3, SNAP-25, and HTR1B in the etiology of ADHD.

Yet, even these associations are small and consistent with the idea that the genetic vulnerability to ADHD is mediated by many genes of small effect. These small effects emphasize the need for future candidate gene studies to implement strategies that will provide enough statistical power to detect such small effects. One such strategy, examination of refined phenotypes that may reduce heterogeneity, is beginning to bear fruit but more research is needed to extend the work focused on ADHD subtypes (eg, inattentive subtype and HTR1B); comorbid psychopathology or cognitive impairment (eg, depression and SNAP-25, reading disability and ADRA2A), and gene-environment interactions (eg, prenatal or psychosocial risk factors for ADHD and SLC6A3). It is also possible that ADHD genetics research will benefit from the study of

endophenotypes such as neuropsychological functioning or brain imaging.[164–166] The ongoing efforts to develop larger collaborative studies with adequate sizes for genome-wide association studies will also be critical in understanding the molecular genetics of ADHD.

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