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Support for Association Between ADHD and Two Candidate Genes: *NET1* and *DRD1*

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Attention deficit hyperactivity disorder (ADHD) is a common, multifactorial disorder with significant genetic contribution. Multiple candidate genes have been studied in ADHD, including the norepinephrine transporter (NET1) and dopamine D1 receptor (DRD1). NET1 is implicated in ADHD because of the efficacy of atomoxetine, a selective noradrenergic reuptake inhibitor, in the treatment of ADHD. DRD1 is primarily implicated through mouse models of ADHD. DNA from 163 ADHD probands, 192 parents, and 129 healthy controls was used to investigate possible associations between ADHD and polymorphisms in 12 previously studied candidate genes (*5-HT1B*, *5-HT2A*, *5-HT2C*, *ADRA2A*, *CHRNA4*, *COMT*, *DAT1*, *DRD1*, *DRD4*, *DRD5*, *NET1*, and *SNAP-25*). Analyses included case-control and family-based methods, and dimensional measures of behavior, cognition, and anatomic brain magnetic resonance imaging (MRI). Of the 12 genes examined, two showed a significant association with ADHD. Transmission disequilibrium test (TDT) analysis revealed significant association of two NET1 single nucleotide polymorphisms (SNPs) with ADHD ($P \leq 0.009$); case-control analysis revealed significant association of two DRD1 SNPs with ADHD ($P \leq 0.008$). No behavioral, cognitive, or brain MRI volume measurement significantly differed across NET1 or DRD1 genotypes at an alpha of 0.01. This study provides support for an association between ADHD and polymorphisms in both NET1 and DRD1; polymorphisms in ten other candidate genes were not associated with ADHD. Because family-based and case-control methods gave divergent results, both should be used in genetic studies of ADHD.

KEY WORDS: attention deficit hyperactivity disorder (ADHD); norepinephrine transporter (NET1); dopamine D1 receptor (DRD1); association study; replication

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset disorder characterized by symptoms of inattention and/or hyperactivity-impulsivity [American Psychiatric Association, 1994]. Estimates of the prevalence of the disorder range from 1.7% to 21% [Acosta et al., 2004], though more conservative estimates range from 5% to 10% [Scahill and Schwab-Stone, 2000]. Heritability estimates based on twin and adoption studies average about 0.8 [Faraone and Biederman, 1998], suggesting that genetic factors play a large role in the etiology of ADHD and giving rise to a host of genetic studies.

ADHD is a complex disorder whose genetic etiology likely involves multiple genes of moderate effect [Smalley, 1997]. Accordingly, over 30 candidate genes have been studied in ADHD [Bobb et al., 2004], yet the literature contains more non-replications than positive findings of association, suggesting that multiple replications are necessary before credence is given to association between any specific marker and ADHD.

As part of an ongoing study of the neurobiology of ADHD [Castellanos et al., 2002], we screened a total of 12 previously reported ADHD candidate genes, including *5-HT1B*, *5-HT2A*, *5-HT2C*, *ADRA2A*, *CHRNA4*, *COMT*, *DAT1*, *DRD1*, *DRD4* (published earlier, see Castellanos et al., 1998), *DRD5*, *NET1*, and *SNAP-25*, in a sample of 163 probands, 192 parents, and 129 healthy controls. Because findings from family-based and case-control based studies are sometimes divergent [Holmes et al., 2000; Qian et al., 2003], we conducted both types of analyses. We also included quantitative behavior and brain magnetic resonance imaging (MRI) measures in our analyses. This was prompted by three lines of evidence: (a) a dimensional approach may be more powerful than a categorical approach for studying genetic associations in ADHD [Bobb et al., 2004]; (b) biological endophenotypes may relate more directly to gene function [Weinberger, 1999; Skuse, 2001]; and (c) ADHD probands (including those in this study) show morphological brain abnormalities when compared to controls [Castellanos et al., 2002; Durston, 2003]. Finally, given evidence that low

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intelligence quotient (IQ) and ADHD may have shared genetic influences [Kuntsi et al., 2004], we extended previous studies by including analyses of cognitive measures.

MATERIALS AND METHODS

Participants

Children and adolescents with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [American Psychiatric Association, 1994] defined ADHD were recruited locally and nationally. Fifty-three percent of the probands were male, and most were Caucasian (75% Caucasian, 12% African American, 10% Hispanic, 2% Asian, and 1% other); their average age was 9.02 ± 2.22 years. Exclusion criteria were a full-scale IQ below 80, evidence of medical or neurological disorders from examination or history, or any other primary Axis I psychiatric disorder. The majority (94%) of probands were diagnosed with ADHD combined type, while 6% were diagnosed with primarily inattentive type. Sixty-six percent participated in a 12 week NIMH study that included school and therapy 5 days a week, as well as a double-blind drug trial (see Sharp et al., 1999). Psychiatric diagnoses were based on the Diagnostic Interview for Children and Adolescents (DICA)-Child, Adolescent, and Parent versions, revised [Reich, 2000]. Other measures included the Conners Parent and Teacher Rating Scales [Werry et al., 1975], Child Behavior Checklist, Teacher Report Form [Achenbach, 1991], Full Scale Wechsler Intelligence Scale for Children, Third Edition (WISC-III) [Wechsler, 1991], a computerized response inhibition task [Casey et al., 1993], and an anatomic brain MRI scan (see Castellanos et al., 2002 for details). Whole blood was drawn from all probands, and, when possible, first-degree relatives. A total of 163 ADHD probands and 192 parents were included in the analysis.

We also recruited healthy controls locally and nationally. Of 129 controls, 57% were male, and most were Caucasian (75% Caucasian, 15% African American, 4% Hispanic, 3% Asian, and 2% other); their average age was 15.99 ± 8.13 years. Whole blood was drawn for genetic analysis, and participants underwent an anatomic brain MRI scan (see Giedd et al., 1999 for details).

This study was conducted at the Child Psychiatry Branch of the National Institute of Mental Health (NIMH) in Bethesda, MD. The NIMH institutional review board approved the protocol, and investigators obtained signed informed consents and assents from the parents and minors, respectively.

Genotyping

We studied 20 polymorphisms from 12 genes; detailed polymorphism information is listed in Supplementary Table I (see the online Supplementary Material at http://www.interscience.wiley.com/jpages/1552-4841/suppmat/index.html). Single nucleotide polymorphism (SNP) genotyping with genomic DNA extracted from immortalized lymphoblastoid cell lines was performed using standard methods (see Gornick et al., 2004 for details). Microsatellite and variable number of tandem repeat (VNTR) polymorphism reactions were performed in a 384-well format in a total volume of 15 μl, with 5 μl of [2 ng/μl] genomic DNA, 9 μl of TrueAllele™ PCR Premix (Applied Biosystems, Inc., Foster City, CA), and 1 μl of [5 μM] pooled DAT1, DRD5, and SNAP-25 primers (ordered from Qiagen, Inc., Valencia, CA). A thermal cycler (PE 9700; Applied Biosystems) heated plates at 50°C for 5 min; 35 cycles of 95°C for 15 sec, 65°C for 30 sec, and 72°C for 30 sec; and 72°C for 15 min. Next, 5 μl of the PCR product, 0.26 μl of GeneScan™ 500-LIZ™ size standard (Applied Biosystems), and 7.74 μl of formamide were transferred to 96-well plates, which were placed in the ABI PRISM® 3100-Avant Genetic Analyzer (Applied Biosystems). Plates were analyzed using GENOTYPER® (Applied Biosystems) software.

Statistics

We checked for Mendelian errors with the program Pedcheck [O'Connell and Weeks, 1998]. None of the SNPs deviated from Hardy–Weinberg Equilibrium. We used the phase known transmission disequilibrium test (TDT), where counts of allele transmissions from heterozygous parents at each SNP locus were analyzed with the TDTPHASE program version 2.37 [Dudbridge, 2003]. We also used the E–M algorithm in TDTPHASE for unknown phase haplotype estimation. The program COCAPHASE [Dudbridge, 2003] was used for case-control comparisons. QTPHASE [Dudbridge, 2003] was used for quantitative trait association analyses.

We investigated possible effects of genotype, and genotype by diagnosis interaction, on 11 brain volume measures (total cerebral volume [TCV], total gray matter, total white matter, cerebellum, caudate, and white and gray components of the frontal, parietal, and temporal lobes) for the four SNPs that showed significant association with ADHD in our sample. We first checked volume measures for normality and homogeneity of variance across diagnostic groups. Sex and age differences across groups were checked with χ^2 and t tests, respectively. We ran two sets of 44 separate analyses of covariance (ANCOVAs): 11 separate analyses with each brain volume measure as the dependent variable, repeated with each of the four positive SNP genotypes (based on TDT and case-control analyses) as independent variables. In the first set, the genotype variable had three categories (e.g., G/G vs. G/A vs. A/A); in the second set, the genotype variable had two categories (e.g., G/G and G/A vs. A/A). For all SNPs, we grouped the homozygous common allele genotype with the heterozygous genotype, and compared that to the homozygous rare allele genotype. The grouped genotypes were not significantly different from one another for any volume measurement in the ADHD, normal control, or combined samples (data not shown). Diagnosis was also included as an independent variable, and age and TCV were included as covariates. Finally, given the large number of tests, we chose an alpha of 0.01.

RESULTS

Case-Control and Family-Based Analyses

For DRD1, ADHD probands were more likely than controls to have the C allele of rs4532 and the A allele of rs265981 (OR = 1.63, $P = 0.006$; and OR = 1.61, $P = 0.008$, respectively). For NET1, there was preferential transmission of the C allele of rs998424 and the T allele of rs3785157 to ADHD probands (relative risk = 1.96, $P = 0.009$; and relatively risk = 2.28, $P = 0.002$, respectively). All other polymorphisms were non-significant (see Table I). To limit the number of tests, only these four positive SNPs were included in subsequent cognitive, behavioral, and brain MRI analyses.

Cognitive and Behavioral Measures

Because ethnic differences significantly correlated with 9 of the 23 cognitive and behavioral measures (data not shown), we included only Caucasians in these analyses (n = 74 probands). The risk alleles of the NET1 SNPs rs998424 and rs3785157 were associated with higher performance on the similarities subtest of the WISC-III, and decreased hyperactivity on the Conners Teachers Rating Scale, respectively ($P = 0.04$); the risk alleles of the DRD1 SNPs rs4532 and rs265981 were each associated with decreased reaction time on the computerized response inhibition task ($P = 0.02$, and

TABLE I. Case-Control and Family-Based Analyses of NET1 and DRD1 in ADHD

		Case-control (n = 163 cases, 129 controls)				Family-based (n = 82 triads, 28 dyads)			
		Risk allele frequency							
Gene	Polymorphism	Probands	Controls	Odds ratio	*P* value	Risk allele transmitted	Risk allele not transmitted	Relative risk	*P* value
NET1 (SLC6A2)	rs998424	0.69	0.70	0.98	0.91	43	22	1.96	0.009
	rs3785157	0.70	0.71	1.03	0.87	41	18	2.28	0.002
DRD1	rs4532	0.39	0.28	1.63	0.006	38	31	1.23	0.40
	rs265981	0.38	0.28	1.61	0.008	38	29	1.31	0.27
5-HT1B	rs6296	0.74	0.70	1.06	0.22	29	24	1.21	0.49
	rs6298	0.75	0.70	1.29	0.18	24	17	1.41	0.27
5-HT2A	rs6313	0.61	0.60	1.04	0.82	44	42	1.05	0.83
	rs6311	0.41	0.40	1.01	0.96	43	47	0.91	0.67
	rs6314	0.11	0.09	1.19	0.49	9	14	0.64	0.30
5-HT2C	rs6318	0.67	0.65	1.03	0.65	9	7	1.29	0.62
ADRA2A	rs1800544	0.71	0.63	1.41	0.05	34	27	1.26	0.37
CHRNA4	rs6090384	0.91	0.90	1.23	0.47	11	10	1.10	0.83
	rs2273505	0.91	0.90	1.12	0.71	13	8	1.63	0.27
	rs2273506	0.08	0.07	1.12	0.72	13	8	1.63	0.27
COMT	rs4680	0.52	0.47	1.11	0.27	48	46	1.04	0.84
DAT1	rs6347	0.28	0.23	1.22	0.17	22	30	0.73	0.27
	VNTR[a]	0.27	0.25	1.12	0.47	20	12		0.16
DRD5	Microsatellite[b]	0.45	0.46	0.93	0.91	28	27		0.89
SNAP-25	Microsatellite[c]	0.57	0.57	0.99	0.88	27	20		0.31

VNTR, variable number of tandem repeats.
[a]Forty base pair VNTR, exon 15.
[b]$(CA)_n$ repeat, 5′-untranslated region.
[c]$(ATTT)_n$ repeat, 5′-untranslated region.

$P = 0.03$, respectively). However, none reached significance at the chosen alpha level of 0.01; thus given the large number of tests, we consider these results likely type I errors.

Anatomic Brain MRI Measures

There were complete genotype and MRI data for 114 ADHD probands and 79 controls. While there were no significant sex differences between controls and probands, controls were significantly older than probands (mean difference = 1.4 years, $t = 2.9$, $P < 0.01$); thus age was included as a covariate in all ANCOVAs. TCV was also included as a covariate in all ANCOVAs, given evidence of smaller overall brain volume in ADHD probands versus controls [Castellanos et al., 2002]. Comparisons across genotype groups showed no significant differences in any of the 11 brain volume measurements. Further, no significant genotype by diagnosis effects were seen (data not shown).

DISCUSSION

Based on a review of molecular genetic studies of ADHD [Bobb et al., 2004], we tested 20 polymorphisms from 12 candidate genes in a sample of 163 probands and 129 controls; only polymorphisms from NET1 and DRD1 were significant. While our sample size does not meet theoretical recommendations for adequate power in association studies of genes of modest effect [Risch and Merikangas, 1996], it is above the average family-based and case-control sample sizes of the ADHD genetics literature [Bobb et al., 2004]. Interestingly, the number of prior published replications for candidate genes did not predict which genes showed positive association with ADHD in our sample, indicating that molecular genetic research in ADHD should continue to investigate (and reinvestigate) a broad spectrum of candidate genes, and supporting the heterogeneity of this disorder.

Our findings provide the first replications of association for both NET1 and DRD1 in ADHD. NET1 is involved in the synaptic reuptake of norepinephrine (NE) [Schomig et al., 1989], which is implicated in ADHD given its association with attention, learning, and memory [Biederman and Spencer, 1999]. More specifically, tricyclic antidepressants and atomoxetine, both of which have proven effective in treating ADHD, target the reuptake of NE [Donnelly et al., 1986; Spencer et al., 1998; Barr et al., 2002].

Indirect evidence that the dopamine (DA) system is involved in ADHD comes primarily from the efficacy of stimulants in treating the disorder. For example, methylphenidate inhibits DA reuptake, thus increasing the amount and duration of DA in the synapse [Amara and Kuhar, 1993]. Moreover, meta-analyses have shown that other DA receptor genes (e.g., *DRD4* and *DRD5*) are part of the genetic etiology of ADHD [Faraone et al., 1999; Lowe et al., 2004]. DRD1 is of interest given that three separate strains of mice with D_{1A} abnormalities show ADHD-like behavior [Clifford et al., 1998; Karasinska et al., 2000; Sagvolden, 2000; Viggiano et al., 2002]; and D1 receptors are abundant in prefrontal cortex, which may be impaired in ADHD [Hall et al., 1994; Arnsten, 2001; Castellanos, 2001].

Three groups have investigated an association between NET1 and ADHD [Barr et al., 2002; McEvoy et al., 2002; Knight et al., 2003; De Luca et al., 2004], with only one reporting positive findings [Knight et al., 2003]. Knight et al. with 180 cases and 334 controls, found significantly different allele frequencies in six NET1 SNPs, including the two studied here. Though, we found transmission distortion for rs998424 and rs3785157, we were not able to replicate allele frequency differences between cases and controls, perhaps due to less power given our smaller sample size.

Two groups have studied DRD1 and ADHD [Kirley et al., 2002; Misener et al., 2004]. Misener et al. found a trend towards overtransmission of the C and A alleles from rs4532 and rs265981, respectively; and significant overtransmission

of a four-SNP haplotype which included those two SNPs [Misener et al., 2004]. While we were unable to replicate this association using a family-based approach, we did find a significantly higher frequency of the risk alleles in our cases as compared to controls.

Other groups in psychiatric genetics have found discrepant results using case-control and family-based methods [Holmes et al., 2000; Roman et al., 2001; Chowdari et al., 2002]. One possible explanation for our discrepancies is that the case-control findings are spurious due to population stratification [Roman et al., 2001]. Our cases and controls were matched for sex and ethnicity; however, controls were significantly older than probands ($t = 10.47$, $P < 0.01$). Even so, population stratification due to a 7-year difference in age is unlikely. Further, secondary case-control analyses of DRD1 SNPs using only Caucasians revealed results similar to those from primary analyses; though, consistent with a reduction in power due to a 25% decrease in sample size, the findings were less significant ($P = 0.07$). Describing similarly divergent results from case-control and family-based methods in a study of DRD4 and ADHD, Holmes et al. discussed the possibility that the risk allele may be more common in the probands excluded from TDT but included for case-control analyses [Holmes et al., 2000]. Yet, as in Holmes et al., this is not the case in our sample.

We did not find any significant effects of our positive SNPs on cognitive or behavioral measures. The putative advantage of utilizing more subtle dimensional measures of ADHD over categorical diagnoses may have been mitigated by lower power, given that we reduced our sample by 30% by limiting the quantitative trait analyses to Caucasians only. While ADHD and low IQ may have shared genetic origins [Kuntsi et al., 2004], there is little evidence specifically implicating NET1 in cognitive dysfunction, and only indirect evidence for DRD1. D_1 receptors in monkey prefrontal cortex are involved in working memory [Goldman-Rakic, 1998], yet both the digit span and arithmetic WISC-III subtests, the best surrogates for working memory in our cognitive assessment, did not significantly vary across DRD1 genotypes. Finally, our ADHD sample had a somewhat elevated IQ (mean full scale $IQ = 109 \pm 15$) as compared to other reports of ADHD cases [Crosbie and Schachar, 2001; Rucklidge and Tannock, 2001]; thus these genes may affect IQ in ADHD samples with more typical cognitive levels.

Analyses of 11 anatomic brain MRI measures did not reveal any significant differences across NET1 or DRD1 genotypes. A preliminary analysis of cortical thickness using a method developed at the Montreal Neurological Institute [MacDonald et al., 2000; Kabani et al., 2001] found differences in right and left superior parietal cortex across DRD1 genotypes, yet those cortical areas were thicker in probands with the DRD1 alleles associated with ADHD. As this is opposite of what we expected, given evidence of thinner cortex in ADHD probands versus controls [Rapoport et al., unpublished data], this finding may represent type I error. However, there is evidence for increased D1 receptor binding in the superior parietal cortex of subjects with schizophrenia versus controls [Domyo et al., 2001]; thus we plan to further investigate the role of DRD1 in this cortical area using longitudinal brain MRI measures.

In summary, we present the first replication supporting the previously described association between ADHD and polymorphisms in NET1 and DRD1. Our findings are limited in that each gene was replicated using a different study design (family-based versus case-control) than was previously reported; dimensional measures of ADHD were not significantly associated with the risk alleles; and these data are not corrected for multiple tests, as it is not yet clear how best to do this. Moreover, we confined our analyses to only previously reported polymorphisms; other polymorphisms from the candidate genes reported here may have been associated with the disorder. Given the results of the current study, along with previous reports and credible evidence from neurobiological and animal models, further studies of the association of ADHD with candidate genes *NET1* and *DRD1* are warranted.

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