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Association of Attention-Deficit Disorder and the Dopamine Transporter Gene

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Summary

Attention-deficit hyperactivity disorder (ADHD) has been shown to be familial and heritable, in previous studies. As with most psychiatric disorders, examination of pedigrees has not revealed a consistent Mendelian mode of transmission. The response of ADHD patients to medications that inhibit the dopamine transporter, including methylphenidate, amphetamine, pemoline, and bupropion, led us to consider the dopamine transporter as a primary candidate gene for ADHD. To avoid effects of population stratification and to avoid the problem of classification of relatives with other psychiatric disorders as affected or unaffected, we used the haplotype-based haplotype relative risk (HHRR) method to test for association between a VNTR polymorphism at the dopamine transporter locus (DAT1) and DSM-III-R–diagnosed ADHD ($N = 49$) and undifferentiated attention-deficit disorder (UADD) ($N = 8$) in trios composed of father, mother, and affected offspring. HHRR analysis revealed significant association between ADHD/UADD and the 480-bp DAT1 allele (χ^2 7.51, 1 df, $P = .006$). When cases of UADD were dropped from the analysis, similar results were found (χ^2 7.29, 1 df, $P = .007$). If these findings are replicated, molecular analysis of the dopamine transporter gene may identify mutations that increase susceptibility to ADHD/UADD. Biochemical analysis of such mutations may lead to development of more effective therapeutic interventions.

Introduction

Attention-deficit disorder is a prevalent disorder, of childhood onset, characterized by attentional dysfunction. It most commonly occurs with impulsivity and hyperactivity, in the form of attention-deficit hyperactivity disorder (ADHD) (American Psychiatric Association 1994). ADHD often persists into adulthood and is a risk factor for development of antisocial and drug-abuse disorders (Mannuzza et al. 1993). Family/genetic studies of ADHD have revealed an increased prevalence of ADHD in relatives of probands with ADHD, compared with relatives of normal or psychiatric controls (Cantwell 1972; Biederman et al. 1990, 1992). There is an increase in attentional dysfunction in genetic parents of probands with hyperactivity, compared with adoptive parents of probands with hyperactivity (Alberts-Corush et al. 1986). In addition, twin studies are consistent with moderate-to-high heritability of attentional dysfunction (Stevenson 1992).

Previously, ADHD was found to be more common in subjects with generalized resistance to thyroid hormone (GRTH), compared with controls (Hauser et al. 1993). However, the prevalence of GRTH in ADHD has been found to be extremely rare (Weiss et al. 1993), and subsequent studies have not supported genetic linkage of ADHD and GRTH (Weiss et al. 1994).

The most commonly used and well-studied treatment approach for ADHD is pharmacotherapy, which is effective in most children with ADHD (reviewed in Greenhill 1992). Pharmacological agents that inhibit the dopamine transporter (including methylphenidate, dextroamphetamine, pemoline, and bupropion) have been shown in numerous, double-blind trials to be effective in the treatment of attentional dysfunction, hyperactivity, and impulsivity of ADHD (Casat et al. 1987; Zametkin and Rapoport 1987; Greenhill 1992; Hechtman 1994; Rapport et al. 1994). This led us to consider the dopamine transporter locus (DAT1) as a primary candidate gene in ADHD.

Although diagnosis of ADHD in probands is reliable after decades of refinement, relatives of probands with ADHD are at increased risk for several disorders other than ADHD (Biederman et al. 1990). For example, in the genetic analysis of ADHD, one is left with the question of whether to consider relatives to be affected or unaffected if they have conduct disorder, mood disorder,

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or alcoholism but do not have a clinical diagnosis of ADHD. Nonparametric methods of genetic analysis have the advantage of not requiring pedigrees with several affected members.

Association studies in which affected individuals are compared with controls suffer from the potential pitfall of sampling controls and affected individuals from populations with different allele frequencies, particularly if the controls and affected individuals are not selected from the same population. The original association found between ADHD (as well as alcoholism, Tourette disorder, and autistic disorder) and the dopamine D2 receptor gene (DRD2) (Comings et al. 1991) suffered from this major methodological weakness. To avoid the potential effects of population stratification, we used the haplotype-based haplotype relative risk (HHRR) method to test for association between a VNTR polymorphism at DAT1 and DSM-III-R (*Diagnostic and Statistical Manual of Mental Disorders,* 3d ed. rev.)–diagnosed ADHD ($N = 49$) and undifferentiated attention-deficit disorder (UADD) ($N = 8$) in trios composed of father, mother, and affected offspring.

Subjects and Methods

Subjects

Consecutive patients seen in the Hyperactivity, Attention, and Learning Problems (HALP) Clinic at the University of Chicago between 20 April 1993 and 18 October 1994 were screened for possible inclusion in the study. The inclusion criteria were (1) a child or adolescent with a DSM-III-R diagnosis of ADHD or UADD, made in a consensus diagnostic conference in which a child psychologist(s), child psychiatrist, and developmental pediatrician presented findings from each of their evaluations; (2) availability of one or more biological parents; and (3) consent to blood collection and participation in this study, from parent(s) and child. UADD is a DSM-III-R diagnosis in which children have attentional problems and distractibility but do not have a sufficient number of symptoms of hyperactivity and impulsivity to meet DSM-III-R criteria for diagnosis of ADHD.

Fifty-six families participated in the study. Because of the unavailability of some of the parents, 24 families consisted of the mother and affected child, 4 families consisted of father and affected child, 27 families consisted of mother, father, and affected child, and 1 family consisted of mother, father, and two affected children. There were 47 families in which the proband had ADHD, 1 family in which two probands had ADHD, and 8 families in which the proband had UADD. The mean age of the probands was 9.4 years (range 4–17 years). Forty-seven probands were Caucasian, 9 were African American, and 1 was Hispanic. Mean family socioeconomic status (Hollingshead and Redlich 1958) was 2.5 (range 1–5). Thirty-eight children (67%) had a comorbid DSM-III-R diagnosis (see table 1). Overall intelligence was average, but there were weaknesses in arithmetic and coding, which were expected, because attention is required for performance on those subtests (see table 2). Behavior-rating scales were consistent with the clinical diagnoses of ADHD or UADD and are summarized in table 2 to describe the severity of symptoms of the subjects.

Table 1

Comorbid Diagnoses

Comorbid Diagnosis	No. of Patients
Axis I:	
Oppositional defiant disorder	19 (33.3%)
Conduct disorder	6 (10.2%)
Anxiety disorder	5 (8.8%)
Elimination disorder	4 (7.0%)
Major depressive disorder	1 (1.8%)
Dysthymia	1 (1.8%)
Axis II:	
Developmental coordination and/or expressive writing disorder	16 (31.4%)
Developmental expressive and/or receptive language disorder	8 (14.0%)
Articulation disorder	4 (7.0%)
Developmental reading disorder	6 (10.2%)
Developmental arithmetic disorder	3 (5.3%)

Procedures

Clinical assessment procedures.—Intelligence was assessed with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), for the 4–5-year-old children, and with the Wechsler Intelligence Scale for Children, 3d edition (WISC-III), for the subjects 6–16 years old (Wechsler 1967, 1991). Several parent and teacher rating scales were obtained prior to the evaluation. Parents completed the Achenbach Child Behavior Checklist (CBCL) (Achenbach and Edelbrock 1983) and Conners Parent Rating Scale—Revised (Goyette et al. 1978). The CBCL and ADD-H: Comprehensive Teacher's Rating Scale (ACTeRS) (Ullmann et al. 1984) were completed by teachers. Diagnoses of ADHD, UADD, or either ADHD or UADD comorbid with conduct disorder or oppositional defiant disorder were based upon multidisciplinary team consensus following a 6-h evaluation that included a semistructured diagnostic interview by a clinical psychologist or child and adolescent psychiatrist, physical and neurological examinations by a developmental pediatrician, and a review of all instruments by at least three experienced clinicians.

Table 2

Psychometric Testing and Behavior-Rating Scales

Scale	No.	Mean ± SD
WISC-III or WPPSI:		
Full-scale	52	97.6 + 13.0
Verbal	51	98.6 ± 12.2
Performance	51	99.9 ± 14.3
Arithmetic	39	8.5 ± 2.7
Coding	36	8.3 ± 2.9
ACTeRs (T score):	39	
Attention		38.3 ± 9.0
Hyperactivity		36.7 ± 13.4
Social skills		39.9 ± 9.4
Oppositional		41.6 ± 9.8
Conners PSQ Parent Rating Scale—Revised (T score):	44	
Conduct problems		69.5 ± 20.4
Learning problem		84.0 ± 18.2
Psychosomatic		62.8 ± 23.9
Impulsive-hyperactive		69.2 ± 13.2
Anxiety		56.7 ± 13.7
Hyperactivity index		75.6 ± 16.0
CBCL (T score):		
Internalizing (parent rating)	48	62.9 ± 12.4
Externalizing (parent rating)	48	66.2 ± 11.4
Internalizing (teacher rating)	38	58.0 ± 9.0
Externalizing (teacher rating)	38	63.1 ± 10.1

DAT1 VNTR analysis.—DNA was extracted from whole blood or normal saline mouth rinse by a Tris-EDTA extraction method. The following primers were used to amplify the region flanking the DAT1 40-bp VNTR: T3-5Long (5'-TGTGGTGTAGGGAACGGCCTGAG-3') and T7-3aLong (5'-CTTCCTGGAGGTCACGGCT-CAAGG-3') (Vandenbergh et al. 1992). The primers were synthesized on an Applied Biosystems 380B DNA synthesizer at the Cancer Research Center at the University of Chicago. Hot-start PCR was carried out in a 75-μl vol containing 400 ng of genomic template, 0.5 M of each primer, 200 μM of each dNTP (dATP, dCTP, dGTP, and dTTP), 1 × PCR buffer, 2 μM $MgCl_2$, and 2 units of *Taq* Polymerase (Amplitaq; Perkin Elmer Cetus). PCR gems (Perkin Elmer Cetus) were added to each sample, and a hot start of 80°C for 5 min and 25°C for 2 min was performed. The template and *Taq* polymerase were added following the hot-start step. Samples were processed in a Perkin Elmer Cetus DNA thermal cycler, through 40 cycles of 30 s at 95°C, 30 s at 68°C, and 1.5 min at 72°C. Samples were stored in a −80°C freezer after the completion of PCR. Two microliters of six-fold–concentrated (Savant vacuum drier) PCR product was mixed with 2 μl of loading buffer (0.05% bromophenol blue and 0.05% xylene cyanol FF). One microliter of the resulting products was then separated at 15°C on 20% homogeneous acrylamide PhastGels with native buffer strips (0.88 M L-alanine, 0.25 M Tris, pH 8.8) on PhastSystem (Pharmacia Biotech). Each gel contained a 100-bp ladder (Gibco BRL/Life Technologies). The PhastGel was prerun at 400 V, 10 mA, 2.5 W for 100 V-h. Samples were applied during a step of 400 V, 10 mA, 2.5 W for 2 V-h. Samples were then separated at 400 V, 10 mA, 2.5 W for 100 V-h. Gels were then silver-stained by using 75 ml of the following reagents: 20% trichloroacetic acid fixing solution for 5 min at 20°C; 5% glutardialdehyde sensitization solution for 6 min at 40°C; triple-distilled water for 2 min (twice) at 40°C; 0.4% silver nitrate for 6 min at 30°C; triple-distilled water for 2.5 min and then 0.5 min at 20°C; triple-distilled water for 0.5 min at 30°C; 2.5% sodium carbonate and 0.1% formaldehyde developing solution for 0.5 min and then 2.5 min at 30°C; 5% glacial acetic acid for 5 min at 30°C; and 12% glycerol and 5% acetic acid preserver solution for 3 min at 30°C. For confirmation, 78 of 141 samples were also run on 4% agarose (Perkin Elmer Cetus) to verify the results observed on the PhastSystem media. Two investigators (M.D.K. and D.M.O.) blindly and independently scored the resulting bands on each gel. Discrepancies were resolved by repetition of PCR using purified template. DNA extracted from whole blood was spun at 3,000 *g* for 12 min in a Microcon-100 microconcentrator (Amicon). The vials were then placed upside down and were spun at 1,000 *g* for 3 min. This template was then used in PCR and gel analysis as described above, with the exception that a combined annealing/extension step of 72°C for 2.5 min was substituted for the separate annealing and extension steps of 68°C and 72°C during PCR.

Results

To avoid the confounding effects of population stratification, we tested the independence of transmission of each parental allele, using HHRR. Whatever the frequency of alleles in the parents of a group of affected offspring is, the chance that each allele will be transmitted to an offspring is 50%, given the null hypothesis of no linkage disequilibrium ($\delta = 0$; no association). If the transmission of an allele deviates from this ratio, on the basis of a standard χ^2 test, evidence for association exists (Rubinstein et al. 1981). A haplotype-based approach was used because of its greater power to detect a genetic association (Ott 1989).

Although there is a VNTR at DAT1, allele frequency in the total parental sample was 1.2% 200-bp alleles (3 copies of VNTR), 22.6% 440-bp alleles (9 copies), and 76.2% 480-bp alleles (10 copies). Genotypes for parent-child pairs and trios are presented in table 3.

Table 3

Genotypes of Combinations of Parent-Child Trios and Pairs

Observed Parental Genotype	Child's Genotype				
	200/480	440/440	440/480	480/480	480/520
Trios (two parents and child):					
200/480 × 480/480			1		
440/480 × 440/480			1	4	
440/480 × 480/480			5	10	
480/480 × 480/480				8	
Parent-child pairs:					
200/480			1		
440/440			3		
440/480	1	3	2	2	
480/480			3	12	1

The 200-bp allele was combined with the less common, 440-bp allele, for HHRR analysis. (The 200-bp allele was not transmitted from a mother and father with genotype 200/480 bp to two unrelated children with genotype 480/480 bp.) HHRR analysis revealed significant association between ADHD/UADD and the 480-bp DAT1 allele (χ^2 7.51, 1 df, $P = .006$) (see table 4). (Two mother-child pairs consisted of heterozygotes, and therefore the transmission status of each of the mothers' alleles could not be determined for HHRR). Similar results were found if only the 47 Caucasian probands were included (χ^2 4.55, 1 df, $P = .033$). If only the 49 ADHD probands are considered, the results are essentially unchanged (HRRR χ^2 7.29, 1 df, $P = .007$).

Discussion

This study presents preliminary evidence of association between ADHD and the dopamine transporter gene. However, it is possible that the association is due to a yet to be discovered ADHD-susceptibility gene in linkage disequilibrium with DAT1. Previously, association was reported between DRD2 and alcoholism (Blum and Noble 1990; Comings et al. 1991), but these findings were not replicated (Kelsoe et al. 1989; Gelernter et al. 1991, 1993; Gejman et al. 1994). A previous association reported between ADHD and DRD2 has not been replicated, and it is likely that it was an artifact of the same population stratification that led to the nonreplicated finding of association between alcoholism and DRD2 (Comings et al. 1991; Gelernter et al. 1993). The current study was designed to address the limitation of the nonreplicated alcoholism study, by using the HHRR to avoid false-positive association due to population stratification. One caveat about the current study is that 24 fathers and 4 mothers are missing from our pedigrees. As in any study, replication in an independent sample is necessary.

Previous studies using the same marker did not find a significant association between DAT1 and schizophrenia (Byerley et al. 1993) or between DAT1 and polysubstance abuse (Persico et al. 1993). Although ADHD is a risk factor for development of substance abuse, approximately four-fifths of children and adolescents with ADHD do not develop substance-use disorders (Mannuzza et al. 1993).

If the finding of association between ADHD and DAT1 is replicated, molecular analysis of the dopamine transporter gene by using screening tools such as PCR-SSCP analysis may identify mutations that increase susceptibility to ADHD and, possibly, to UADD (Orita et al. 1989). Biochemical analysis of such putative mutations may lead to development of more effective therapeutic interventions, by study of the effects of such a mutation on the pharmacology of the dopamine transporter through transfection into cell lines of the putative mutant and wild-type transporters. In addition, a mouse model for ADHD would be feasible, using sequential gene targeting of ES cells (Askew et al. 1993).

If linkage between ADHD and DAT1 is established, it will be important to emphasize the role of the dopamine

Table 4

HHRR, for All Families

	440 bp	480 bp	Total
Transmitted	12	72	84
Not transmitted	27	57	84
Total	39	129	168

NOTE.—χ^2 7.51, 1 df, $P = .006$.

transporter—or another gene in linkage disequilibrium with DAT1—in contributing to susceptibility to ADHD. Although many children in a community are identified as having ADHD, because of behavioral and academic problems, many others are not identified, because they compensate well for attentional dysfunction. Even though ADHD is a risk factor for later development of substance abuse and antisocial disorders, most children with ADHD function well during adulthood. Early identification of risk for ADHD may identify children for preventive multimodal intervention, including parent training, social skills training, psychotherapy, and pharmacotherapy (Hechtman 1993; Ialongo et al. 1993).

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