

Collaborative analysis of DRD4 and DAT genotypes in population-defined ADHD subtypes

Richard D. Todd,¹ Hongyan Huang,¹ Susan L. Smalley,^{2,3} Stanley F. Nelson,^{2,4} Erik G. Willcutt,⁵ Bruce F. Pennington,⁵ Shelley D. Smith,⁵ Stephen V. Faraone,⁶ and Rosalind J. Neuman¹

¹Departments of Psychiatry and Genetics, Washington University School of Medicine, St. Louis, Missouri, USA; ²UCLA Center for Neurobehavioral Genetics, Departments of ³Psychiatry and ⁴Human Genetics, Neuropsychiatric Institute University of California, Los Angeles, USA; ⁵Department of Psychology, University of Colorado, Boulder, Colorado, USA; ⁶Medical Genetics Research Program, Department of Psychiatry SUNY Upstate Medical University, Syracuse, New York, USA

Background: It has been proposed that some of the variability in reporting of associations between attention deficit hyperactivity disorder (ADHD) and candidate genes may result from mixing of genetically heterogeneous forms of ADHD using DSM-IV criteria. The goal of the current study is to test whether population-based ADHD subtypes defined by latent class analysis help resolve issues of variable findings across individual gene association studies. **Methods:** Three studies which had previously reported no associations between polymorphisms of the DRD4 and DAT genes and DSM-IV defined ADHD were reanalyzed using population-based and DSM-IV defined ADHD subtypes. **Results:** Across studies no significant associations were found for either DRD4 or DAT polymorphisms using DSM-IV ADHD subtypes. In contrast, a significant association was found between the combined data set for the 440 base pair 3' DAT VNTR polymorphism and population-defined severe combined ADHD (OR = 1.25, $p = .01$). A marginally significant association was also found between the 7 repeat DRD4 allele and population-defined severe combined ADHD. **Conclusion:** Use of alternative population-based defined ADHD subtypes may help resolve some of the variable results presented for candidate gene association studies in ADHD. **Keywords:** Attention deficit/hyperactivity disorder, DRD4, DAT, latent class analysis. **Abbreviations:** ADHD: attention deficit/hyperactivity disorder; VNTR: variable number of tandem repeats; DRD4: dopamine D4 receptor gene; DAT: dopamine transporter gene; TDT: transmission disequilibrium test.

A major focus of biomedical research for the past 20 years has been the identification of genomic DNA sequence differences that predispose individuals to different disorders. Though there have been numerous successes in the identification of genes for severe, rare Mendelian disorders (that is, autosomal dominant and recessive diseases such as Huntington's disease or cystic fibrosis and x-linked disorders such as fragile-x syndrome), progress has been slower for common disorders including hypertension, type II diabetes mellitus and the psychiatric syndromes. Syndrome is usually taken to mean a collection of signs and symptoms that occur together more frequently than expected by chance. That is, a syndrome is a statistical definition based on the population frequencies of the individual signs and symptoms included in the syndrome. Few of the psychiatric disorders described in DSM-IV or ICD-10 have been shown to satisfy such a population-based definition. The premise of this article is that one source of variability in genetic association studies of attention deficit hyperactivity disorder (ADHD) is the use of non-population-based definitions of who is considered a case by DSM-IV and ICD-10 criteria. In the current study, genotyping results from several

previous reports are reanalyzed using ADHD subtyping based on the clustering of symptoms in general population samples of children and adolescents.

Attention deficit hyperactivity disorder (ADHD) is a common, highly heritable behavioral syndrome which is clinically characterized by problems with attention span, distractibility, hyperactivity and impulsivity (American Psychiatric Association, 1994). Though few population-based tests of the validity of DSM-IV or other ADHD criteria have appeared, the prevalence appears to be 4–12%, affecting boys more commonly than girls. Some studies suggest that the most common form is the predominantly inattentive type.

A variety of investigators have reported genetic association studies on DSM-IV and ICD-10 defined ADHD subtypes or related ADHD conceptualizations. In particular, meta analyses of an exon 3 repeat polymorphism of the dopamine DRD4 receptor gene (Faraone, Doyle, Mick, & Biederman, 2001; Faraone et al., in press; Maher, Marazita, Ferrell, & Vanyukov, 2002) and a 3' flanking variable number of tandem repeats (VNTR) polymorphism of the dopamine transporter DAT gene (Faraone et al., in press; Maher et al., 2002; Purper-Ouakil et al.,

2005) suggest that while marked variability occurs across studies, overall there is support for association of ADHD with dopamine system genes (strong support for the 7 repeat form of the DRD4 exon 3 polymorphism and weaker support for the 480 bp form of the DAT 3' VNTR polymorphism).

Several family studies have supported the concept that DSM-IV defined predominantly inattentive and combined subtypes of ADHD represent the same familial form of illness (Faraone, Biederman, & Friedman, 2000a; Faraone et al., 2000b; Smalley et al., 2000; Todd et al., 2001c). That is, there is increased co-familiality of these two forms of ADHD. In contrast, the DSM-IV predominantly hyperactive/impulsive ADHD subtype appeared to be a distinct familial entity (Faraone et al., 2000a, 2000b; Smalley et al., 2000; Todd et al., 2001c). Part of the problem with detecting family specificity of ADHD subtypes under a DSM-IV type of nomenclature resides in the application of the symptom number cutoff rule to define ADHD subtypes. For example, a child who has a total of 10 ADHD symptoms may be classified as predominantly inattentive (6 inattentive, 4 hyperactive symptoms), predominantly hyperactive/impulsive (4 inattentive and 6 hyperactive/impulsive symptoms) or unaffected (5 inattentive and 5 hyperactive/impulsive symptoms). Though this symptom number criteria has clinical utility (Lahey et al., 1996), this may introduce uncertainty into studies of subtype etiology.

An alternative approach is to determine what DSM-IV ADHD symptoms cluster together in the general population. Whether these population-defined ADHD phenotypes represent distinct genetic entities can be tested by comparing monozygotic/dizygotic twin concordance rates for twins being of the same or opposite ADHD subtype. Latent class analysis of DSM-IV ADHD symptoms in three separate general population-based twin studies has established the presence of eight forms of clustering of ADHD symptoms in girls (Todd et al., 2001c), boys and girls (Rasmussen et al., 2002; Volk, Neuman, & Todd, in press) and in non-twin siblings of twins (Rasmussen et al., 2004). In contrast to results for DSM-IV subtypes, these population-based groupings appear to be independently heritable (Rasmussen et al., 2004; Todd et al., 2001c). Though the DSM-IV combined ADHD subtype is predominantly represented in a single population-defined subtype (severe combined symptoms), DSM-IV defined predominantly inattentive and predominantly hyperactive/impulsive cases are redistributed across several population-based ADHD subtypes (Table 3 and (Rasmussen et al., 2002; Todd et al., 2001c)). This suggests the variability in reporting of specific candidate gene associations with ADHD may be due to differential mixing of independent ADHD syndromes in different studies. To test this hypothesis we reassigned individuals from three studies which had reported lack of association with DRD4 or DAT

polymorphisms and DSM-IV ADHD subtypes (Kustanovich et al., 2004; Palmer et al., 1999; Todd et al., 2001b) to population-defined ADHD groups. Genotyping data were analyzed using family-based methods that extract maximum data available from parents and offspring.

Methods

Samples and population subtype assignment

Through the ADHD Molecular Genetics Network (2000), a request was made for the sharing of existing data sets for the purpose of combined analyses of candidate gene results across studies. Since the planned analyses among members of the Network differed, restrictions were not made on what types of diagnostic evaluations were included (type of interview, Parent Report, Teacher Report, best estimate clinician diagnosis, etc.) but standard reporting of genotypic information and details of evaluations were requested. Of the eight data sets reviewed, five met the requirements that would allow assignment of individual cases to latent class defined ADHD subtypes (i.e., parent report of presence of all 18 DSM-IV ADHD symptoms). Of these five, three of the studies had genotyping information on parents and offspring (a trio) allowing family-based transmission disequilibrium test (TDT) – like analyses to protect from possible stratification artifacts. These three data sets (from the University of Colorado at Boulder (UCB), from the University of California at Los Angeles (UCLA), and from Washington University School of Medicine, St. Louis (WUMS)) contained complete clinical and genotypic information on 2,090 offspring and genotypic information on both biological parents. Details of the design, sampling and diagnostic assessments used for each study can be found in Smalley et al. (2000:UCLA), Todd et al. (2003a:WUSM) and Willcutt et al. (2005:UCB). The UCB and WUSM samples used community-based screening of twins for ADHD while the UCLA study used clinical referred and advertisement-based screening of non-twin siblings for recruitment. Symptom response profiles for the 18 DSM-IV symptoms by parent report were used to post-hoc assign individuals to population-defined ADHD classes using the program LCAP-CA (Neuman et al., 2001) and the profile endorsement probabilities of Rasmussen et al. (2004). Each individual was placed in a latent class if the probabilities indicated that they were at least twice as likely to be a member of that class versus the next most probable class. The average best class assignment probability was .87 (median .91) and ranged from .52 to 1.0. Individuals whose class assignment was ambiguous (i.e., their best class assignment was not at least twice as probable as the second most probable class assignment) were eliminated from further analysis ($n = 54$).

Genotyping

For all three studies similar genotyping methods were used based on the primers originally reported by Cook et al. (1995) for the 3' VNTR of the dopamine transporter gene (DAT) and those of LaHoste et al. (1996) for

the exon 3 48-base pair repeat of the human dopamine DRD4 receptor gene. Samples were not exchanged between laboratories but the allele frequency distributions for both polymorphisms were nearly identical for three samples.

Statistical analyses

Genetic associations were estimated using the program Transmit (Version 2.5.4) (Clayton, 1999). This program allows estimation of genetic associations from the probability of allele transmission to an affected offspring when there may be uncertain marker allele assignment. For each ADHD subtype alleles were aggregated with frequencies of less than 1% and multiple cases within a given family were allowed. For monozygotic twin pairs, only one twin was included (26% of WUMS sample and 13% of UCB sample). All possible allele types were considered and *p*-values were estimated using bootstrapping approaches with 2,000 iterations. We ignored findings if the expected number of transmitted alleles was less than or equal to 5. Analyses were also run for the 'high risk' DRD4 7 repeat allele versus all others and the 'high risk' 3' DAT 480 base pair repeat versus all others.

Results

Total sample and individual sample characteristics are displayed in Table 1 for DSM-IV subtypes and in Table 2 for population-defined ADHD subtypes. There were a total of 2,090 individual offspring included in the analyses (Table 1). Of these, 1,352 had no ADHD DSM-IV diagnosis, 316 were primarily inattentive subtype, 54 were primarily hyperactive/impulsive subtype, and 368 were combined subtype. Fifty-four individuals had ambiguous assignments to the population-based subtypes and were removed from further analyses (Table 2). Overall, the sample was primarily male, with significantly more males in the DSM-IV defined ADHD subtypes. The sample

was predominantly of self-identified Northern European ancestry and there were no significant differences by DSM-IV or population-defined ADHD subtypes with respect to ethnic/racial distribution. Of particular note, 456 offspring in the DSM-IV no diagnosis class were reassigned to an ADHD subtype in the latent class criteria other than the few symptoms class. As shown in Table 4, as previously described by Todd and colleagues (Rasmussen et al., 2002; Todd et al., 2001c), only 39% of the DSM-IV predominantly inattentive type individuals were reassigned to the severe attention problems subtype while 74.5% of DSM-IV combined type individuals were assigned to the severe combined problems subtype. Only 54 individuals had DSM-IV predominantly hyperactive/impulsive type and 50% of these were assigned to the severe hyperactive/impulsive problems subtype.

Genotypic data for the DRD4 exon 3 48-base pair repeat polymorphism and for the DAT 3' flanking VNTR polymorphisms were analyzed for both DSM-IV and latent class ADHD subtypes. In contrast to previously reported meta analyses of these polymorphisms (Curran et al., 2001; Faraone et al., 2001, in press; Maher et al., 2002), but in keeping with individual reports for these samples (Kustanovich et al., 2004; Palmer et al., 1999; Todd et al., 2001a), no significant association was found for polymorphisms of either gene with DSM-IV defined ADHD or ADHD subtypes (data not shown). There was a trend for significant over-transmission of the 480 base pair DAT allele ($p = .10$) and under-transmission of the 440 base pair allele ($p = .09$) for the DSM-IV combined ADHD subtype in the total sample (data not shown). Furthermore, no individual study results were significant for DSM-IV ADHD or subtypes when analyzed by all alleles or only 'high risk' alleles versus all other alleles combined.

Table 1 Sample characteristics of ADHD: DSM-IV subtypes

	DSM-IV subtype	Number of individuals	Sex (%)		Average age (yrs)		Race (%)	
			Male	Female	Male	Female	Caucasian	Non-Caucasian
Total combined 2,090	None	1,352	56.1	43.9	13.1	12.8	84.0	16.0
	Inattentive	316	75.9	24.1	12.3	11.1	85.7	14.3
	Hyperactive	54	74.1	25.9	9.3	10.2	90.7	9.3
	Combined	368	79.9	20.1	11.5	10.0	80.4	19.6
Total UCB 48	None	23	73.9	26.1	10.0	14.2	78.3	21.7
	Inattentive	22	68.2	31.8	11.2	10.7	80.0	20.0
	Hyperactive	0	–	–	–	–	–	–
Total UCLA 432	Combined	3	0.0	100.0	–	8.3	33.3	66.7
	None	78	48.7	51.3	12.7	12.6	81.8	18.2
	Inattentive	135	67.4	32.6	10.8	10.9	84.4	15.6
	Hyperactive	30	73.3	26.7	7.5	9.4	90.0	10.0
Total WUSM 1,610	Combined	189	76.2	23.8	10.4	9.6	75.1	24.9
	None	1,251	56.3	43.7	13.2	12.8	84.2	15.8
	Inattentive	159	84.3	15.7	13.4	11.6	87.4	12.6
	Hyperactive	24	75.0	25.0	11.4	11.3	91.7	8.3
	Combined	176	85.2	14.8	12.5	11.0	86.9	13.1

Table 2 Sample characteristics of ADHD: population-defined subtypes

	Population-based subtype	Number of individuals	Sex (%)		Average age (yrs)		Race (%)	
			Male	Female	Male	Female	Caucasian	Non-Caucasian
Total combined 2,036	1-FEW	934	51.6	48.4	13.5	13.1	86.0	14.0
	2-MIA	230	75.6	24.4	13.0	12.1	83.5	16.5
	3-TALK	74	51.4	48.6	12.3	12.6	87.8	12.2
	4-MCMB	205	72.2	27.8	11.5	11.2	80.5	19.5
	5-MHI	57	77.2	22.8	13.6	11.3	80.7	19.3
	6-SCMB	332	76.5	23.5	11.2	10.1	79.2	20.8
	7-SIA	163	77.3	22.7	12.8	11.3	85.8	14.2
	8-SHI	41	70.7	29.3	9.9	11.3	73.2	26.8
Total UCB 40	1-FEW	8	50.0	50.0	10.3	15.8	87.5	12.5
	2-MIA	7	71.4	28.6	9.6	11.0	85.7	14.3
	3-TALK	0	–	–	–	–	–	–
	4-MCMB	7	57.1	42.9	8.3	10.0	71.4	28.6
	5-MHI	1	100.0	0.0	14.0	–	0.0	100.0
	6-SCMB	5	20.0	80.0	15.0	8.5	60.0	40.0
	7-SIA	12	83.3	16.7	11.5	9.5	72.7	27.3
	8-SHI	0	–	–	–	–	–	–
Total UCLA 386	1-FEW	58	43.1	56.9	14.0	13.4	80.7	19.3
	2-MIA	6	66.7	33.3	9.3	12.0	50.0	50.0
	3-TALK	1	100.0	0.0	15.0	–	100.0	0.0
	4-MCMB	54	68.5	31.5	9.7	9.5	87.0	13.0
	5-MHI	0	–	–	–	–	–	–
	6-SCMB	202	76.7	23.3	10.6	9.5	75.7	24.3
	7-SIA	50	66.0	34.0	11.0	11.6	86.0	14.0
	8-SHI	15	60.0	40.0	6.8	9.8	80.0	20.0
Total WUSM 1,610	1-FEW	868	52.2	47.8	13.5	13.0	86.3	13.7
	2-MIA	217	76.0	24.0	13.2	12.1	84.3	15.7
	3-TALK	73	50.7	49.3	12.3	12.6	87.7	12.3
	4-MCMB	144	74.3	25.7	12.3	12.1	78.5	21.5
	5-MHI	56	76.8	23.2	13.6	11.3	82.1	17.9
	6-SCMB	125	78.4	21.6	12.1	11.3	85.6	14.4
	7-SIA	101	82.2	17.8	13.6	11.1	87.1	12.9
	8-SHI	26	76.9	23.1	11.3	12.7	69.2	30.8

¹Abbreviations: FEW = few symptoms class; MIA = moderate inattentive symptom class; TALK = talkative symptom class; MCMB = moderate combined symptom class; MHI = moderate hyperactive/impulsive class; SCMB = severe combined symptom class; SIA = severe inattentive symptom; SHI = severe hyperactive/impulsive.

As shown in Table 4 for the major alleles of the DAT gene and population-based ADHD subtypes, there were significant associations for the severe combined ADHD subtype with *over*-transmission of the DAT 440 base pair allele and *under*-transmission of the 480 base pair allele ($p = .01$). There were

no significant associations for other population-based subtypes with this polymorphism. When analyzed by individual study, the same association was found for the WUSM and UCLA samples but was only independently significant for the UCLA sample (Table 5).

Table 3 Cross tabulation of ADHD subtypes by DSM-IV and population-defined criteria

Population Defined Subtype ¹	DSM-IV				Total
	None	Inattentive	Hyperactive	Combined	
1-FEW	896	19	4	15	934
2-MIA	173	42	2	13	230
3-TALK	67	1	3	3	74
4-MCMB	83	67	13	42	205
5-MHI	44	7	2	4	57
6-SCMB	25	37	0	270	332
7-SIA	42	110	0	11	163
8-SHI	13	0	24	4	41
Ambiguous	9	33	6	6	54
Total	1352	316	54	368	2090

¹Abbreviations: FEW = few symptoms class; MIA = moderate inattentive symptom class; TALK = talkative symptom class; MCMB = moderate combined symptom class; MHI = moderate hyperactive/impulsive class; SCMB = severe combined symptom class; SIA = severe inattentive symptom class; SHI = severe hyperactive/impulsive class.

Table 4 Results of transmit analysis of DAT and DRD4 in population-defined ADHD subtypes for the combined data set

Population-defined subtype ¹	DAT 440 bp allele			DAT 480 bp allele			DRD4 allele 4			DRD4 allele 7		
	Observed	Expected	<i>p</i>	Observed	Expected	<i>p</i>	Observed	Expected	<i>p</i>	Observed	Expected	<i>p</i>
1-FEW	222	220.9	.89	705	709.4	.60	618	623.6	.59	204	198.8	.57
2-MIA	49	50.7	.73	165	164.3	.88	141	145.8	.34	46	46.2	.95
3-TALK	18	15.5	.31	46	48.5	.31	41	43.5	.34	17	14.3	.18
4-MCMB	68	69.9	.73	176	173.4	.63	153	153.3	.95	58	55.8	.62
5-MHI	23	22.9	.97	51	51.1	.97	45	48.4	.25	12	9.7	.23
6-SCMB	157	141.4	.01	354	369.9	.01	339	349.7	.18	111	101.8	.16
7-SIA	60	63.9	.39	174	169.9	.36	155	155.5	.91	37	38.0	.78
8-SHI	15	15.9	.74	42	40.6	.59	33	36.6	.17	13	11.7	.57

¹Abbreviations: FEW = few symptoms class; MIA = moderate inattentive symptom class; TALK = talkative symptom class; MCMB = moderate combined symptom class; MHI = moderate hyperactive/impulsive class; SCMB = severe combined symptom class; SIA = severe inattentive symptom; SHI = severe hyperactive/impulsive.

Table 5 Summary of results for population-defined severe combined ADHD at the DAT and DRD4 loci by site

Site	DAT 440 bp allele		DAT 480 bp allele		DRD4 allele 4		DRD4 allele 7	
	Odds ratio	<i>p</i> -value	Odds ratio	<i>p</i> -value	Odds ratio	<i>p</i> -value	Odds ratio	<i>p</i> -value
UCB	–	–	1.02	.81	.91	.73	–	–
UCLA	1.29	.007	.90	.006	.96	.46	1.24	.14
WUSM	1.15	.46	.96	.47	.90	.14	1.12	.63
Combined	1.25	.01	.92	.01	.94	.18	1.20	.16

In contrast, Table 4 shows marginally significant evidence for over-transmission of the 7 repeat DRD4 allele and under-transmission of the 4 repeat DRD4 allele in the severe combined ADHD subtype ($p = .16$). A similar direction of results was found for all three studies and the DRD4 4 and 7 repeat alleles (Table 5).

Discussion

Though overall, the preponderance of published data are consistent with the involvement of dopamine pathway genes in the etiology of ADHD, there has been considerable variability in the reporting of results for the DRD4 and DAT genes (Curran et al., 2001; Faraone et al., 2001, in press; Maher et al., 2002), with some reporting evidence of sample heterogeneity (Curran et al., 2001) and others not (Faraone et al., 2001; Maher et al., 2002). This has been particularly true for the DAT gene (Purper-Ouakil et al., 2005). Though a variety of factors may contribute to the heterogeneity of reported results for these loci, an under-explored source of error is diagnostic heterogeneity of ADHD which may represent underlying genetic heterogeneity (Todd, 2000, 2002).

In this report DRD4 and DAT genotyping results from three studies that had failed to demonstrate significant associations with DSM-IV defined ADHD were reanalyzed using population-derived ADHD subtypes. The novel result of the current study is the detection of an overall significant and study-specific association of the 440 base pair 3' DAT VNTR allele with the population-defined severe combined symp-

tom ADHD subtype. Previous studies have focused on the over-transmission of the 480 base pair allele in ADHD. Outside of the current study, only three other reports of transmission disequilibrium-based analyses have presented results for the 3' DAT 440 base pair VNTR allele. Two of these reports show under-transmission of the 440 base pair allele (Barr et al., 2001; Cook et al., 1995) while one found over-transmission (Holmes et al., 2000) for DSM-IV defined ADHD. All three studies included predominantly DSM-IV combined subtype ADHD. Whether these 3' polymorphisms are functional is debatable but the findings of this study suggest that use of population-defined ADHD subtypes, which appear to be genetically independent (Rasmussen et al., 2004; Todd et al., 2001c), may resolve some of the variability of reports of association studies with this gene. If the 3' VNTR polymorphisms of the DAT gene are functional, then the impact of the 440 and 480 base pair alleles may vary depending on the genetic background of the populations studied. It is also possible that the VNTR alleles are in linkage disequilibrium with other functional DNA sequence variations which have not yet been identified. Taken in combination with the previous demonstration of association of CHR4 polymorphisms with population-defined severe inattentive ADHD but not with DSM-IV predominantly inattentive ADHD subtype (Todd et al., 2003a), the current results offer preliminary validation that these population-defined ADHD subtypes may have different genetic associations. Both the DAT and CHR4 genes modulate synaptic dopamine levels as would be predicted by the dopamine theory of ADHD (Levy, 1991).

Though the current results and those of Todd et al. (Todd, Lobos, Sun, & Neuman, 2003b) support the use of population-defined ADHD subtypes for both candidate genes in genetic linkage studies of ADHD, the current results have limitations. First and foremost, a minority of the studies deposited with the ADHD network provided sufficient data for the use of population-based ADHD subtypes in a TDT analysis. Hence, it is possible that different association results would have been found if these other studies were included. Second, the limited size of the Colorado sample precluded detection of study-specific effects for this group.

The concept of identifying and using population-derived phenotypes in genetic or other studies of child and adolescent psychopathology has application beyond the study of ADHD. As noted in the introduction, few of the common psychiatric disorders in DSM-IV or ICD-10 have been validated at the population level. By definition, such population-derived phenotypes are more symptomatically homogeneous. To the extent that the identification of such naturally occurring clusters of signs and symptoms represent more etiologically pure forms of disorder, such subtyping approaches will increase the power of etiological and treatment studies.

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Correspondence to

Richard D. Todd, Washington University School of Medicine, Departments of Psychiatry and Genetics, 660 South Euclid Avenue, Campus Box 8134, St. Louis, Missouri 63110, USA; Tel: (314) 747-6769; Fax: (314) 747-6777; Email: toddr@psychiatry.wustl.edu

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