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Association of ADHD, tics, and anxiety with dopamine transporter (*DAT1*) genotype in autism spectrum disorder

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Abstract

Background—Autism spectrum disorder (ASD) is associated with high rates of psychiatric disturbance to include attention-deficit/hyperactivity disorder (ADHD), tic disorder, and anxiety disorders. The aim of the present study was to examine the association between a variable number tandem repeat (VNTR) functional polymorphism located in the 3'-untranslated region of the dopamine transporter gene (*DAT1*) and the severity of these symptoms as well as the association between the *DAT1* *DdeI* polymorphism and severity of tics.

Methods—Parents ($n = 62$) and teachers ($n = 57$) completed a DSM-IV-referenced rating scale for 67 children with ASD.

Results—According to parent ratings, children with the 10-10 repeat allele (versus a combined group of all other genotypes) exhibited less severe symptoms of hyperactivity and impulsivity as well as less severe language deficits. Teacher ratings indicated that social anxiety and tic symptoms were more severe for children with the 10-10 genotype versus all others. Exploratory analyses provided preliminary support for the notion that heterozygosity (9–10 repeat genotype) may be a risk/protective factor. There were no associations of tic severity with the *DAT1* *DdeI* polymorphism.

Conclusion—Collectively, these results suggest that the extraordinary variability in ASD clinical phenotypes may be explained in part by the same genes that are implicated in a host of other psychiatric disorders in non-ASD populations. Nevertheless, replication with independent samples is necessary to confirm this preliminary finding.

Keywords

Autism; Asperger's syndrome; PDD-NOS; autism spectrum disorder; attention-deficit/hyperactivity disorder; impulsivity; social anxiety; dopamine; dopamine transporter gene; genetics; Tourette syndrome

The core features of autism spectrum disorder (ASD) include deficits in functional language and social skills, as well as repetitive behaviors, all of which vary greatly in severity, complexity, and co-occurrence. The three most common subtypes of ASD are autism

(deficits in all three areas), Asperger's syndrome (primarily social deficits and repetitive behaviors), and PDD-NOS (clinically significant symptoms but sub threshold for autism or Asperger's syndrome). It is estimated that approximately .6% of the general population has the disorder (Fombonne, 2005), and it is much more common in males than females. As a group, children with ASD exhibit high rates of behavioral disturbance (e.g., Goldstein & Schwabach, 2004; Lee & Ousley, 2006; Leyfer et al., 2006). For example, many meet DSM-IV symptom criteria for attention-deficit/hyperactivity disorder (>50%) (Gadow, DeVincent, & Pomeroy, 2006), anxiety disorder (>50%) (Gadow, DeVincent, Pomeroy, & Azizian, 2005), and motor and vocal tic disorder (>60%) (Gadow & DeVincent, 2005); therefore, comorbidity is inevitably high. Although these behavioral syndromes appear to be phenomenologically similar to traditional non-ASD psychiatric disorders and often lead to pharmacotherapy and social isolation (Aman, Lam, & Van Bourgondien, 2005) and family stress (Herring et al., 2006), relatively little is known about their etiology (e.g., Brieber et al., 2007; Gadow, DeVincent, & Schneider, in press; Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008; Smalley et al., 2002). Traditionally, it has been assumed they were linked in some way to the pathogenesis of ASD and, therefore, genetic studies have logically focused on the core features of ASD (reviewed by Grice & Buxbaum, 2006; Yang & Gill, 2007).

Dopamine system genes are likely candidates for the study of behavioral syndromes within the ASD clinical phenotype because they are implicated not only in ASD (e.g., Dawson et al., 2005; Previc, 2007; Toda et al., 2006), but also in its behavioral concomitants, such as ADHD (reviewed by Li, Sham, Owen, & He, 2006), tic disorder (e.g., Singer et al., 2002), and social anxiety (e.g., Sareen et al., 2007). One gene of considerable interest is solute carrier family 6, member 3 (*SLC6A3*), also known as dopamine transporter gene (*DAT1*). *DAT1* encodes a sodium dependent dopamine transporter that mediates reuptake of the neurotransmitter at the synapse. The 3'-untranslated region of *DAT1* contains a 40bp variable number tandem repeat (VNTR), existing in 3 to 13 copies. The 9- and 10-repeat alleles are the two most common variants in Caucasian, Hispanic and African-American samples. Expression studies indicate that the *DAT1* VNTR is a functional polymorphism, with significantly higher levels of DAT1 produced from the 10-repeat allele than the 9-repeat allele (Fuke et al., 2001), but findings are mixed (see Brookes et al., 2007). Another dopamine transporter polymorphism of interest is DAT1 *DdeI*, recently reported to be associated with Tourette syndrome (Yoon et al., 2007). Specifically, a diagnosis of Tourette syndrome was found to be associated with the DAT1 *DdeI* polymorphism AG versus AA.

A number of studies have investigated the relationship between *DAT1* polymorphisms and behavioral syndromes in individuals who do not have ASD and have found that the 10-repeat allele or the 10-10 repeat genotype is associated with ADHD (reviewed by Yang et al., 2007), anxiety and tics (Comings et al., 1996; Rowe et al., 1998). Nevertheless, others report that the 9-repeat allele (e.g., Todd et al., 2005; Young et al., 2002) may be a risk factor for ADHD. Lee et al. (2007) have also suggested the possibility that the risk factor for disruptive behavior symptoms, including ADHD, is heterozygosity, i.e., differentially higher levels in heterozygotes (9-10 repeat genotype) versus homozygotes (9-9 or 10-10 repeat genotypes).

The present study examined the association between *DAT1* genotype and severity of ADHD, social anxiety, and tic symptoms in children with diagnosed ASD. Because a dimensional model of psychopathology has both statistical and conceptual advantages over a categorical model (e.g., Szatmari et al., 2007), we used a validated DSM-IV-referenced behavior rating scale for defining relevant psychiatric symptom dimensions (i.e., component phenotypes and not psychiatric diagnoses). Owing in part to a lack of prior research on behavioral syndromes in ASD, this study is by necessity descriptive (i.e., hypothesis generating and not hypothesis confirming). Based on prior research with non-ASD samples, we predicted that the 10-10 *DAT1* genotype would be associated with more severe ADHD, tics, and anxiety symptoms compared with a combined group of all other genotypes. Because it has been hypothesized that ASD is associated with hyperdopaminergic functioning (reviewed by Previc, 2007), it was also conceivable that ASD pathogenic factors might alter these expected outcomes. However, evidence supporting a ‘hyperdopamine model’ of ASD is at best mixed (reviewed by Lam, Aman, & Arnold, 2006). Owing to the fact that parents and teachers often identify different children in the same sample as having ADHD or other clinical phenotypes (Gadow et al., 2004, 2006), we predicted that informant would be an important variable in understanding gene–behavior relations. Lastly, exploratory analyses were conducted to investigate potential gene–ASD symptom associations and the possibility of heterozygosity as a risk genotype for ADHD (see also Comings & MacMurray, 2000).

Materials and methods

Participants

Families of consecutive referrals to a university hospital developmental disabilities specialty clinic located on Long Island, New York, with at least one child with a diagnosis of ASD were contacted by mail for participation in a genetic study. A total of 92 individuals were initially recruited, but to maximize homogeneity the study sample ($N = 67$) was limited to individuals who were children (4–14 years old) when the diagnostic and behavioral evaluations were conducted. Parent/teacher ratings of psychiatric symptoms were available for 62/57 of the children, respectively. Demographic characteristics are presented in Table 1. This study was approved by a university Institutional Review Board, informed consent was obtained, and appropriate measures were taken to protect patient (and rater) confidentiality.

Diagnoses of ASD were made by an expert clinician with more than 20 years of clinical and research experience with ASD. These diagnoses were based on five sources of information about ASD symptoms to verify DSM-IV criteria: (a) comprehensive developmental history of language and social development and inflexible or repetitive behaviors (which was obtained from a structured questionnaire completed by the parent prior to the intake evaluation), (b) clinician interview with child and caregiver(s), (c) direct observations of the child in the clinic, (d) review of standardized parent- and teacher-completed rating scales that included validated ASD subscales from the Child Symptom Inventory-4 (CSI-4; Gadow & Sprafkin, 2002), and (e) prior evaluations by educators and clinicians. In addition, the Autism Diagnostic Observation Schedule (Lord et al., 2000) and/or Autism Diagnostic Interview-Revised (Rutter, Le Couteur, & Lord, 2003) were administered by trained staff and were used to confirm ASD diagnoses.

Procedure

Behavioral evaluations—Prior to scheduling their initial clinic evaluation, the parents of potential participants were mailed a packet of materials including behavior rating scales for both parent and teacher, background information questionnaire, and permission for release of school reports, psycho-educational, and special education evaluation records. Rating scales included parent and teacher versions of the CSI-4. Parents were required to complete and return their forms as well as distribute school materials prior to the first appointment. In most cases, ratings were completed by the child's mother. Intake evaluations included interviews with the children and their caregivers; informal observation of parent-child interaction; and review of the aforementioned measures.

Genotyping DAT1 polymorphisms—VNTR repeat status was determined using DNA isolated from peripheral blood cells and polymerase chain reaction (PCR). Amplifications were performed in a 50 μ l volume with primers almost identical to those described by Congdon, Lesch, and Canli (2008): DAT1F-CTTCCTGGAGGTCACGGCTCAAGG and DAT1R- TGCGGTGTAGGGAACGGCCTGAG. Each reaction mixture contained 50ng DNA, 200 μ M dNTP, 1 μ M of each primer, 1.25 U HotMaster Taq polymerase, and 1XHotMaster buffer. Cycling conditions began with an initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 62.8°C for 30 sec, and extension at 72°C for 30 sec followed by a final extension at 72°C for 10 min. Products were analyzed with an HDA-GT12 Genetic Analyzer (eGene Inc.) and genotype analysis conducted by an investigator (J.R.) who was blind to the behavioral characteristics of the study sample. A control DNA sample, previously sequence confirmed to have the 10-10 repeat genotype, was amplified alongside the other samples (in a separate tube), serving both as a positive control and assisting in allele calling on gels.

Single-nucleotide polymorphism (SNP) analysis was performed with high-resolution melting. PCR was carried out in a 10 μ l volume with primers DAT1SNPF-CATCATCTACCCGGAAGCCAT and DAT1SNPR-GATA CCCAGGGTGAGCAGCAT. Each amplification was overlaid with mineral oil and contained 20ng of DNA, .25 μ M of each primer, and 1X LightScanner Master Mix (Idaho Technology Inc). Reaction conditions began with a denaturation at 95°C for 2 min, followed by 40 cycles of 94°C for 30 seconds and 72.9°C for 30 seconds. Melt analysis was performed between 80 and 98°C with a LightScanner (Idaho Technology, Inc.) (Liew et al., 2004; Zhou et al., 2004) and SNP status determined using the Small Amplicon Module. One individual with each genotype (AA, AG, GG) was sequenced to confirm accuracy of the high-resolution melt analysis (data not shown).

Measures

The CSI-4 (Gadow & Sprafkin, 1986, 2002) has both parent and teacher versions. Individual items bear one-to-one correspondence with DSM-IV symptoms (i.e., high content validity). To assess symptom severity, items are scored (never = 0, sometimes = 1, often = 2, and very often = 3) and summed separately for each symptom dimension. In the present study, primary analyses pertained to ADHD (inattention, hyperactivity, impulsivity), social (teacher ratings only) and generalized anxiety, and tics. Exploratory analyses included the

three ASD symptom dimensions (social deficits, language deficits, repetitive behaviors). Numerous studies indicate that the CSI-4 demonstrates satisfactory psychometric properties in community-based normative, clinic-referred non-ASD, and ASD samples (Gadow & Sprafkin, 2007).

Statistical analyses

Chi-square tests (categorical variables) and ANOVAs (continuous variables) were used for group comparisons. For primary analyses, children homozygous for the 10-repeat allele were compared to a group comprised of all other genotypes. Age, gender, SES, and ASD subtype were not significantly correlated with severity of ADHD, anxiety, or tics. To gauge the magnitude of group differences, effect size (percentage of variance in dependent variables accounted for by independent variables) was calculated using partial eta-squared (η^2). A rule of thumb for determining the magnitude of η^2 suggests the following: .01–.06 = small, .06–.14 = moderate, and >.14 = large (Cohen, 1988). Exploratory analyses were conducted to investigate possible associations with ASD dimensions and the possibility that heterozygosity was the risk genotype for ADHD. For these analyses, children were separated into three groups (i.e., 10-10 vs. 9-10 vs. 9-9 repeat alleles).

Results

Genotypes

The distribution of *DAT1* genotypes (frequencies/percents) was 10-10 repeats (29/43.3%), 9-10 repeats (29/43.3), 9-11 repeats (1/1.5%), 10-11 repeats (1/1.5%), and 9-9 repeats (7/10.4%). For primary analyses, individuals homozygous for the 10-repeat allele were compared to all others; thus, 29 (43%) of the children fell into the *DAT1* 10-10 repeat group and 38 (57%) were in the *DAT1* non-10-10 group. Comparisons between the two groups indicated no significant differences in age, gender, IQ, ethnicity, SES, single-parent household, special education services, ever or current medication use, or ASD subtype (Table 1). The distribution of alleles and genotypes is comparable to non-ASD samples (e.g., Congdon et al., 2008; Lee et al., 2007; Yoon et al., 2007). The percentages of *DAT1 DdeI* genotypes were AA (55%), AG (35%), and GG (10%), which are highly similar to Yoon et al.'s (2007) control sample.

ADHD

Analyses indicated significant group differences for parent ratings of the severity of both hyperactivity and impulsivity symptoms of ADHD. These symptoms were significantly less severe for children who were homozygous for the 10-repeat allele versus youngsters in the non-10-10 repeat group (Table 2). Although teacher ratings of both hyperactivity and impulsivity symptoms also appeared less severe for the 10-10 repeat group, these differences did not reach statistical significance.

Tics

Teacher ratings of motor tics were more severe for the 10-10 repeat group versus the non-10-10 repeat group and the magnitude of this difference was large (Table 2). Vocal tics

were also rated more severely for children in the 10-10 repeat group than for those in the non-10-10 repeat group. Parent ratings of tics were not significant.

There were no associations between DAT1 *DdeI* polymorphism for parent or teacher ratings of motor, vocal, or total tics, even when controlling for ADHD severity. Nor was the DAT1 *DdeI* polymorphism associated with any other symptom rating.

Anxiety

Teachers also rated symptoms of social anxiety more severely for children in the 10-10 repeat group than those in the non-10-10 repeat group (Table 2). There were no significant group differences for parent or teacher ratings of generalized anxiety.

Exploratory analyses

There was some evidence that *DAT1* genotype may be associated with severity of the core features of ASD. Parent ratings of ASD language deficits were more severe for the non-10-10 ($M = 7.5$; $SD = 3.0$) than the 10-10 ($M = 5.4$; $SD = 3.7$) repeat groups ($F = 5.71$, $p = .02$, $\eta^2 = .09$). Teacher ratings were nonsignificant.

Analyses of the three group comparison (i.e., 10-10 vs. 9-10 vs. 9-9 genotypes) found significant group differences for parent ratings of impulsivity symptoms of ADHD. Post hoc analyses indicated that the heterozygous 9-10 repeat group exhibited more severe impulsivity than the homozygous 10-10 repeat group (Figure 1). These results suggest that the *DAT1* heterozygous genotype may be associated with *more* severe impulsive (and possibly hyperactive) symptoms.

Discussion

To the best of our knowledge this is one of the first molecular genetic studies to investigate behavioral syndromes (i.e., component phenotypes) within the ASD clinical phenotype. Our results support dopamine dysregulation as one possible contributing factor in the pathogenesis of behavioral disturbance in this clinical population and are internally consistent for several dimensions of behavioral pathology. Nevertheless, we emphasize the fact that replication with independent samples is necessary to confirm these preliminary findings. Specifically, we found that the distribution of *DAT1* genotypes in our sample was similar to non-ASD samples, and that youngsters with at least one 9-repeat allele (primarily 9-10 and 9-9 genotypes) were rated by their mothers as exhibiting more severe symptoms of hyperactivity and impulsivity than children who were homozygous for the 10-repeat allele. At first blush this appears to be at odds with several studies of non-ASD samples indicating the opposite relation (reviewed by Li et al., 2006); however, if ASD can be characterized by hyperdopaminergic brain activity as some (e.g., Gillberg & Svennerholm, 1987) but not all (Narayan, Srinath, Anderson, & Meundi, 1993) studies suggest, then our findings for ADHD could be interpreted as being consistent with an equilibration mechanism (e.g., Barthelemy et al., 1988). In other words, the 10-10 genotype may actually have a normalizing or 'protective' effect for at least some individuals with ASD, but for now this is a matter of speculation. Exploratory analyses revealed a pattern of results that were compatible with those of Lee et al. (2007); namely, the means for our two homozygous groups (9-9 and

10-10) were similar, suggesting that the risk factor for impulsivity (and possibly hyperactivity) may be heterozygosity (9-10 repeat genotype). However, as was the case for the Lee et al. (2007) study, we were not able to draw any firm conclusions about the 9-9 repeat genotype owing to its relative rarity. Nevertheless, we believe this issue warrants further study.

Teacher ratings of ADHD symptoms did not evidence associations with the risk genotype. We also found similar informant differences for the MAO-A VNTR promoter polymorphism in a subgroup of boys from the same sample (Roohi et al., 2008). Here, the risk genotype was associated with only parent ratings of ADHD. This outcome is likely linked to the fact that in a given sample the two informants often identify different children as exhibiting the ADHD clinical phenotype (e.g., Gadow et al., 2004). Several other genetic studies of ADHD have also reported very different outcomes for parent versus teacher report (reviewed by Thapar, Langley, O'Donovan, & Owen, 2006), but the true extent of this phenomenon or its mechanism(s) is unknown because few investigations actually examine this issue.

Teacher ratings of motor and vocal tic severity were associated with *DAT1* genotype (10-10 > non-10-10), which is consistent with a literature linking Tourette syndrome to dysregulation of dopamine function, particularly over-activity (Singer et al., 2002; Yoon et al., 2007). Similarly, Rowe et al. (1998) reported more severe ratings of tics in their 10-10 (versus non-10-10) sample of non-ASD children. Tarnok et al. (2007), however, found individuals with at least one copy of the 9-repeat allele (i.e., non-10/10 group) were at greater risk of tic severity (measured dimensionally). In the present study it is not known why parent ratings of tics were not associated with genotype. It may be helpful to note, however, that a controlled study of methylphenidate in children with Tourette syndrome found tic improvement with teacher but not parent ratings (Gadow, Sverd, Nolan, Sprafkin, & Schneider, 2007). Lastly, although Yoon et al. (2007) found a differentially greater association of *DAT1 DdeI* polymorphism AG versus AA with a diagnosis of Tourette syndrome in non-ASD individuals, this was not the case in the present study, but we emphasize that additional research with a larger sample will be necessary to confirm our finding in youngsters with ASD.

Results also indicated gene-behavior associations for anxiety and language deficits. Teacher ratings of social anxiety were more severe for the 10-10 genotype, which is in agreement with findings of others (Comings et al., 1996; Rowe et al., 1998) linking *DAT1* genotypes with both social anxiety and tics. Our own study of teacher ratings of 1420 elementary school children also found an association between social anxiety and tic severity that was distinct from co-morbid ADHD (Gadow, Nolan, Sprafkin, & Schwartz, 2002). As for ASD symptoms, parent ratings of language problems were more associated with the non-10-10 genotypes, which is consistent with an ASD hyperdopaminergic hypothesis. Given the facts that (a) IQ and ASD language deficits were minimally correlated ($r = -.18$) in this sample and (b) both genotype groups had similar IQs, the obtained association appears to have something more to do with ASD and not just intellectual ability.

Interpretation of study findings are subject to the following qualifications: We used a dimensional strategy to characterize component phenotypes as compared with categorical diagnoses, so obtained findings may not apply to the latter. The size of the study sample may have limited our ability to detect more gene–behavior associations, therefore, negative findings must be considered tentative. It is also possible that the study sample was not representative; therefore replication in larger samples is necessary before concluding that obtained associations are in fact generalizable. Although the study did address several potential confounds (e.g., age, gender, ethnicity, SES, IQ, medication, single parent), it is possible that the two genotype groups differed with regard to a variable confounded with *DAT1* gene activity. Moreover, future studies may wish to consider potential gender and ethnic differences, interactions with other genes and environmental variables, as well as inclusion of non-ASD comparison samples. Lastly, a satisfactory theoretical explanation for our findings is greatly limited by our lack of knowledge of how *DAT1* VNTR genotypes impact brain development and inconsistencies in the literature regarding ongoing brain activity. The fact that ADHD and anxiety figure strongly in the clinical presentation of both ASD (e.g., Sukhodolsky et al., 2008; Weisbrot, Gadow, DeVincent, & Pomeroy, 2005) and tic disorders (e.g., Gadow, Nolan, et al., 2002; Pierre et al., 1999) and share factors implicated in their pathogenesis including genes involved in brain development and functioning as well as specific brain structures (e.g., Amaral et al., 2003) greatly complicates the picture.

In summary, the observed association of the *DAT1* VNTR polymorphism with ADHD, tics, and social anxiety in children with ASD supports consideration of emotional and behavioral characteristics of individuals with ASD in research design and data analyses. Moreover, inclusion of assessment instruments based on DSM-IV constructs may reveal a wider range of associations with molecular variables. Lastly, extrapolation of findings from non-ASD samples appears to have heuristic value in the study of behavioral syndromes in ASD. Clinically, our results suggest that the use of molecular biology to validate clinical psychiatric phenotypes in children with ASD may ultimately inform nosology, response to treatment, and long-term clinical management.

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Figure 1.
Parent ratings of ADHD symptom severity as a function of *DAT1* genotype

Table 1Descriptive characteristics of study sample ($N = 67$)

Characteristic	10-10 repeat ($n = 29$)		Non-10-10 repeat ($n = 38$)		χ^2	F	p
	F (%)	Mean (SD)	F (%)	Mean (SD)			
Age		6.9 (2.6)		6.8 (2.6)	.01		.933
Gender (male)	26 (90)		32 (84)		.42		.517
IQ ($n = 58$)		76.0 (21.1)		79.7 (25.7)	.33		.566
Caucasian	28 (97)		36 (95)		.13		.722
Special education	25 (86)		31 (82)		.26		.612
Medication							
Current	4 (14)		12 (32)		2.86		.091
Ever	12 (41)		15 (40)		.03		.875
SES ($n = 65$)		42.8 (11.0)		42.0 (12.0)	.01		.788
Single parent	0 (0)		1 (3)		.78		.379
ASD Subtype					.09		.958
Autistic	12 (41)		15 (40)				
Asperger's	6 (21)		9 (24)				
PDD-NOS	11 (38)		14 (37)				

Note: SES = socioeconomic status assessed with Hollingshead's (1975) index of occupational and educational social status; scores range from 24 (unskilled laborers) to 66 (major business and professionals).

Table 2
Differences in severity of psychiatric symptoms between 10-10 genotype and non-10-10 (all other genotypes) groups

Variable	10-10 repeat		Non-10-10 repeat		F	p	η^2	Group differences
	Mean (SD)	(n)	Mean (SD)	(n)				
Parent ratings		(n = 26)		(n = 36)				
ADHD hyperactivity	6.5 (3.9)		8.7 (3.8)		5.27	.025	.08	Non-10-10 > 10-10
ADHD impulsivity	3.5 (2.9)		5.1 (2.9)		4.49	.038	.07	Non-10-10 > 10-10
Motor tics	.7 (.9)		.5 (.8)		.90	.348	.02	
Vocal tics	.8 (1.1)		.8 (.9)		.00	.993	.00	
Teacher ratings		(n = 25)		(n = 32)				
ADHD hyperactivity	5.4 (4.8)		6.2 (4.7)		.39	.533	.01	
ADHD impulsivity	3.5 (3.7)		4.2 (3.4)		.62	.435	.01	
Social anxiety	2.3 (2.0)		1.3 (1.4)		5.50	.023	.09	10-10 > Non-10-10
Motor tics	1.6 (1.4)		.7 (.9)		9.33	.003	.15	10-10 > Non-10-10
Vocal tics	1.3 (1.4)		.7 (.9)		4.11	.048	.07	10-10 > Non-10-10