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Association of a Monoamine Oxidase-A Gene Promoter Polymorphism With ADHD and Anxiety in Boys With Autism Spectrum Disorder

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Abstract

The aim of the present study was to examine the association between a variable number tandem repeat (VNTR) functional polymorphism in the promoter region of the MAO-A gene and severity of ADHD and anxiety in boys with ASD. Parents and teachers completed a DSM-IV-referenced rating scale for 5- to 14-year-old boys with ASD ($n = 43$). Planned comparisons indicated that children with the 4- versus 3-repeat allele had significantly ($p < .05$) more severe parent-rated ADHD inattention and impulsivity, and more severe teacher-rated symptoms of generalized anxiety. Our results support a growing body of research indicating that concomitant behavioral disturbances in children with ASD warrant consideration as clinical phenotypes, but 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; Generalized anxiety disorder; Monoamine oxidase; MAO-A; Genetics

Introduction

Although it has long been established that children with autism spectrum disorder (ASD) frequently exhibit a variety of emotional and behavioral disturbances (Rutter et al. 1967), until very recently these behavioral concomitants were generally considered to be part of the ASD diathesis (American Psychiatric Association, 1994), which to some extent discouraged the search for their biologic substrates. We now know, however, that approximately one-half of children with a diagnosed ASD meet DSM-IV symptom criteria for moderate to severe attention-deficit hyperactivity disorder (ADHD) (Gadow et al. 2004a; 2006) and anxiety disorder (Gadow et al. 2005; Sukhodolsky et al. 2008; Weisbrot et al. 2005) resulting in a highly diverse clinical phenotype. Efforts to validate these behavioral syndromes in children with ASD have generally revealed many similarities with non-ASD samples. For example, youngsters with ASD+ADHD are clearly different from those who do not have the disorder (Gadow et al. 2006), and ADHD is distinguishable from other similar disorders such as oppositional defiant disorder (Gadow et al. in press-a). Moreover, this generalization extends to differences between ADHD subtypes (inattentive, hyperactive-impulsive, combined). Clinically, behavioral disturbances in children with ASD often lead to pharmacotherapy, social isolation, and family stress (Aman et al. 2005; Herring et al. 2006). Although specific genes likely to be implicated in the pathogenesis of ASD are currently being pursued (Grice and Buxbaum 2006), little research has focused on linking concomitant behavioral phenotypes to their biologic substrates.

Monoamine oxidase A (MAO-A) catalyzes the oxidization of three neurotransmitters (dopamine, norepinephrine, serotonin) implicated in the pathogenesis of neurobehavioral disorders. Expression of the enzyme correlates with a 30 bp variable number tandem repeat (VNTR) functional polymorphism 1.2 kb upstream of the MAO-A coding sequence. A VNTR polymorphism in the promoter region of the MAO-A gene is reported to be associated with several psychiatric disorders. The two most common polymorphisms are the 3- and 4-repeat alleles, which are purportedly associated with decreased and increased transcriptional activity, respectively (Sabol et al. 1998). The ratio of 4- versus 3-repeat genotypes is approximately 2:1 in White and in Hispanic/Latino samples. Because the MAO-A gene is located on the X chromosome, males have only one allele. In non-ASD samples, the 4-repeat allele was found to be associated with anxiety (Deckert et al. 1999; Samochowiec et al. 2004), impulsivity (Manuck et al. 2000; Passamonti et al. 2006), and possibly ADHD (Manor et al. 2002), although findings for the latter are mixed (e.g., Brookes et al. 2006; Lawson et al. 2003). Studies of the MAO-A polymorphism in individuals with ASD are limited. Cohen et al. (2003) reported on 45 boys (ages 2–12 years) with autism and found more severe ASD symptoms in individuals with the 3-repeat versus 4-repeat allele; however, the mean IQ score of their subjects with the 3-repeat allele was 20 points lower than their 4-repeat group. In related studies, Yirmiya et al. (2002) found a tendency for lower intellectual ability to be associated with the 3-repeat allele in children with autism, but Jones et al. (2004) did not.

The primary objective of the present study was to examine the potential association between MAO-A genotype and severity of ADHD and anxiety in a restricted age-range of boys with ASD (i.e., to explore behavioral phenotypes within the ASD clinical phenotype). Due to the

statistical advantages of dimensional assessment of component phenotypes (Manor et al. 2002; Szatmari et al. 2007), we used a validated DSM-IV-referenced behavior rating scale to calibrate symptom severity. Based on previously published research with non-ASD samples, we predicted that the 4-repeat allele would be associated with more severe ADHD and anxiety symptoms. Owing in part to a lack of prior research, exploratory analyses were conducted that examined possible associations with other co-occurring psychiatric symptoms as well (i.e., hypothesis generating and not hypothesis confirming). Because parents and teachers often indicate minimally overlapping groups of children as exhibiting specific psychiatric behaviors (e.g., Gadow et al. 2004b), we fully expected that relations between variables would differ by informant and therefore we conducted analyses for parent and teacher ratings of psychiatric symptoms separately.

Materials and Methods

Participants

The families of consecutive referrals to a university hospital developmental disabilities specialty clinic located on Long Island, New York, and who had 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, of whom 44 were boys between 5 and 14 years old when the diagnostic evaluations were conducted. Of these, one was excluded from the sample because the child was determined to have a 5-repeat polymorphism (see section “Procedure”). Limiting the study to Caucasian boys had several methodological advantages to include not having to address homo- versus heterozygosity, possible gender dimorphism in MAO-A activity (Jonsson et al. 2000; Williams et al. 2003), and ethnic differences in the distribution of genotypes. The demographic characteristics of the final sample ($n = 43$) are presented in Table 1. This study was approved by a university Institutional Review Board, 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 and Sprafkin 1986, 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 et al. 2003) were administered by trained staff and were used to confirm ASD diagnoses.

Procedures

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 evaluations 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 (93%), 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 MAO-A Polymorphisms—VNTR repeat status was determined using DNA isolated from peripheral blood cells and polymerase chain reaction (PCR). Primers described by Sabol et al. (1998); namely, MAO APT1 (5'-ACAGCCTGACCGTGGAGAAG-3') and MAO APB1 (5'-GAACGGACGCTCCATTCGGA-3') were used to amplify genomic material in a 50 µl reaction mixture containing 50 ng DNA, 0.2 mM dNTP, 1 mM of each primer, 1.25 U HotMaster Taq polymerase, and 1×HotMaster buffer. The PCR program began with an initial denaturation at 95°C for 5 min, followed by 30 cycles of denaturation at 95°C for 30 s, annealing at 65.4°C for 30 s, and extension at 72°C for 30 s followed by a final extension at 72°C for 10 min. Products were analyzed with an HDA-GT12 Genetic Analyzer (eGene Inc) by an investigator (J.R.) who was blind to the behavioral characteristics of the boys. A control male DNA sample, previously sequenced and confirmed to have three copies of the repeat, was amplified alongside the other samples (in a separate tube), serving both as a positive control and assisting in allele calling on gels.

Measures

Psychiatric Symptoms—The CSI-4 (Gadow and Sprafkin 2002) has both parent and teacher versions. Individual items bear one-to-one correspondence with DSM-IV symptoms (i.e., high content validity). Informants are instructed to rate child's general overall behavior (i.e., characteristic traits). 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, analyses pertained to four symptom dimensions: ADHD inattention (I; 9 items), ADHD: hyperactivity-impulsivity (HI; 9 items), generalized anxiety disorder (GAD; 6 items), and ASD (12 items). Severity of oppositional defiant disorder (ODD; 8 items) and major depressive episode (MDE; 10 items) symptoms were treated as covariates (see section "Statistical Analyses").

Numerous studies indicate that the CSI-4 demonstrates satisfactory psychometric properties in community-based normative, clinic-referred non-ASD, and ASD samples (Gadow and Sprafkin 2007). Validity studies of the parent and teacher versions include comparisons with dimensional rating scales, laboratory measures, chart diagnoses, and structured psychiatric interviews; comparisons between symptomatic and asymptomatic samples and between samples with specific behavioral syndromes; and response to behavioral and pharmacological interventions (Gadow and Sprafkin 2002; 2007). With regard to comparisons to chart diagnoses (Gadow and Sprafkin 2002) and structured psychiatric interviews (Grayson and Carlson 1991; Sprafkin et al. 2002), optimal sensitivity and specificity of parent screening cutoff or symptom severity scores generally ranges from .70 to .90 for ADHD, GAD, and ASD, which according to Cicchetti et al.'s (1995) criteria is fair

to excellent. The findings of several studies show that CSI-4 scores show little relation to age, IQ, or SES, and differences between ASD subtypes in CSI-4 symptom severity has generally been found to be minimal.

Risk/Protective Factors—The Parent Questionnaire contains demographics (e.g., age, gender, ethnicity) and information regarding mental health risk/protective factors: single parent (yes/no); parents' level of education and occupation for calculating Hollingshead's (1975) socio-economic status (SES); current special education (yes/no); and ever and current psychotropic medication (yes/no). IQ scores were obtained from school reports included with the packet materials.

Statistical Analyses

Chi-square tests (categorical variables) and ANOVAs (continuous variables) were used for genotype group comparisons; only statistically significant ($p < .05$) group differences are reported for planned comparisons examining ADHD and anxiety. Because these planned comparisons are, by definition, based on a priori hypotheses supported by previous research, no adjustment was made for multiple comparisons (Rothman 1990). However, for those exploratory analyses that were nominally significant (i.e., without adjustment for multiple comparisons), we also report the Bonferroni-adjusted p -value (to protect against a Type 1 error), but not in the case of non-significant findings (to protect against a Type 2 error). Intermediate results are appropriately noted. Although genotype groups did not differ in terms of ODD and MDE symptom severity, these variables were treated as covariates in the ADHD and GAD analyses, respectively, to control for the potential confound of psychiatric co-morbidity. Demographic variables significantly correlated with the dependent variables were also treated as covariates were indicated. 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). Based on prior research linking MAO-A genotype to impulsivity, secondary analyses were conducted for the subscale scores of the five hyperactivity items and four impulsivity items, separately.

Results

Genotypes

There were 44 boys (5–14 years old) in the genetic study sample with the following polymorphisms: three repeats ($n = 12$; 27%), four repeats ($n = 31$; 69%), and five repeats ($n = 1$; 4%). None had 3.5 repeats. This distribution is similar to that reported by Sabol et al. (1998) for Caucasians and to Cohen et al.'s (2003) sample of autistic children, which was primarily Caucasian. To enhance statistical power by eliminating a third comparison group, the one boy with the 5-repeat allele was excluded from the analyses.

Demographic Differences

Demographics and risk/protective factor data for the sample are shown in Table 1. Comparisons between the two groups of males indicated no significant differences in age,

IQ, ethnicity, SES, single-parent household, special education services, ever or current medication use, or ASD subtype.

Psychiatric Symptoms

Parent Ratings: After controlling for severity of ODD symptoms and SES, results indicated significant group differences for parent ratings of both types of ADHD. ADHD inattentive type symptoms were more severe for boys with the 4-repeat ($M = 18.1$, $SD = 4.9$) versus the 3-repeat ($M = 14.1$, $SD = 5.7$) allele ($F = 4.66$, $p = .04$), and the effect size was moderate ($\eta_p^2 = .12$) (Fig. 1). Similarly, after controlling for ODD severity, ADHD hyperactive-impulsive type symptoms were rated as being more severe in the 4-repeat ($M = 13.1$, $SD = 5.4$) versus the 3-repeat ($M = 8.6$, $SD = 5.1$) allele group ($F = 5.08$, $p = .03$), and the effect size was also moderate ($\eta_p^2 = .12$). There were no significant group differences for parent ratings of GAD symptoms ($\eta_p^2 = .003$).

Teacher Ratings: Analyses showed significant group differences for teacher ratings of GAD, even while controlling for MDD severity and SES (Fig. 1). GAD symptoms were rated as being more severe in the 4-repeat ($M = 3.6$, $SD = 2.5$) versus the 3-repeat ($M = 1.9$, $SD = 1.8$) allele group ($F = 5.03$, $p = .03$), and the effect size was moderate ($\eta_p^2 = .12$). Contrary to parent ratings, however, there were no significant group differences for ADHD:I or ADHD:HI symptoms, although mean scores for ADHD:HI were higher for the 4-repeat genotype ($\eta_p^2 = .03$).

ASD Symptom Severity

There were no significant group differences for parent ($\eta_p^2 = .03$) or teacher ($\eta_p^2 = .007$) ratings of ASD symptom severity.

Secondary Analyses

After controlling for ODD symptom severity, impulsivity symptoms were more severe for the 4-repeat ($M = 5.4$, $SD = 2.9$) than the 3-repeat ($M = 2.9$, $SD = 2.8$) allele group ($F = 5.74$, $p = .02$), and these effects were of moderate magnitude ($\eta_p^2 = .13$). The adjusted alpha level for these analyses was $p = .03$. There were no significant group differences for the parent-rated hyperactivity scale.

Discussion

The finding that parents rated children with the 4-repeat allele as having more severe ADHD inattention and impulsivity symptoms is consistent with Manor et al.'s (2002) report of an association between the 4-repeat allele and performance on a computerized impulsivity task in children with ADHD. Similarly, Passamonti et al. (2006) found that healthy adult males with the 4-repeat allele had higher self ratings of impulsivity and significantly greater brain activity (i.e., abnormal response) in right ventrolateral prefrontal cortex, a brain region associated with inhibitory functions. Children with more severe teacher-rated generalized anxiety symptoms were more likely to have the 4-repeat allele, which is consistent with

findings for anxiety in non-ASD samples (Samochowiec et al. 2004). Collectively, our results suggest that behavioral disturbances in children with and without ASD may share similar pathogenic mechanisms; however, replication with larger samples of ASD children is necessary to confirm these preliminary observations.

Less than perfect concordance in informant report is commonplace in the extant ADHD literature (Gadow et al. 2004b; Gadow et al. 2007; in press-b; Martin et al. 2002; Sherman et al. 1997). Informant disagreement has been attributed to a number of different variables (Achenbach et al. 1987; Boomsma et al. 2005; Gadow et al. 2004b; Hudziak et al. 2005; Offord et al. 1996; Martin et al. 2002), but the salience of specific behaviors is likely linked to caregiver task expectations (Drabick et al. 2008). In the school setting, teachers have access to environmental constraints that are not always available to parents, which can limit the severity of many symptomatic behaviors in some but not necessarily all pupils. In this regard, parents rate hyperactivity-impulsivity in children with ASD more severely than teachers (Gadow et al. 2005). Moreover, teacher concerns are more focused on skill acquisition and classroom discipline. In the home setting, youngsters have greater freedom to chose activities and with less opportunity to disrupt the directed work activities of others.

The exact role of the MAO-A polymorphism in the pathogenesis of ADHD and anxiety is unknown. Although review of relevant research is beyond the scope of a brief report, it is possible that MAO activity impacts impulsivity, for example, through dopaminergic (Congdon et al. 2008) or serotonergic (Evenden 1999; Soubrie 1986) systems. However, the findings of a recent study by Fowler et al. (2007) indicate brain MAO activity does not correspond with MAO-A genotype, which they note suggests a more likely role in brain development. Alternatively, it is also possible that MAO-A genotype is not a functional polymorphism. Other research suggests that serotonin (Devlin et al. 2005) and possibly dopamine (Dawson et al. 2005) system genes and MAO-A promoter polymorphism (Cohen et al. 2003; Jones et al. 2004; Yirmiya et al. 2002) may be implicated in the etiology of ASD. It therefore seems reasonable to speculate that the confluence of genes that produce the structural and functional CNS changes that result in ASD phenotypes also render the individual more vulnerable to other genetic influences whose combined effects on the CNS contribute to the differentially higher severity of psychiatric co-morbidity observed in this clinical population.

Limitations

Our results are subject to the following qualifications: we used a dimensional strategy to characterize behavioral phenotypes as compared with categorical diagnoses, so obtained findings may not apply to the latter. Because the study sample was relatively small, this may have decreased our ability to detect additional genotype group differences. 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 accurate. The patient sample was limited to Caucasian boys, but populations are nevertheless generally heterogeneous in genetic ancestry. Therefore, it is possible that a genetic subgroup(s) within the study sample was over-represented as having both the risk genotype and more severe ADHD or anxiety symptoms (i.e., population stratification), in which case reported

associations may be spurious. Nevertheless, experts disagree as to the significance of this confound. For example, it has been argued that population stratification probably plays only a minor role in the failure to replicate findings of association studies, unless of course study samples are ethnically diverse (reviewed by Cardon and Palmer 2003). Moreover, although the two genotypes were balanced in terms of age, SES, and IQ, it is possible that some measured or unmeasured characteristic for which the groups were not balanced explain our findings, but this is true for all observational studies. Reported gene-behavior associations may be due not to the MAO-A promoter polymorphism, but to another causative allele in linkage disequilibrium with the MAO-A polymorphism. Gene-behavior associations may also vary as a function of environmental experiences (Kim-Cohen et al. 2006). It is likely that the heterogeneity within the ASD clinical phenotype may have underestimated the magnitude of gene-symptom associations, and future research may wish to consider a cohort of individuals with ASD in which the underlying molecular basis is both known and uniform (e.g., boys with Fragile X).

Summary

The association of ADHD and generalized anxiety with the long MAO-A allele is not inconsistent with the expected pattern of predicted associations for non-ASD samples. The most important methodological implications of these findings are (a) consideration of emotional and behavioral characteristics of individuals with ASD in research design and data analyses may enhance the clarity of gene-behavior relations; (b) inclusion of assessment instruments based on DSM-IV constructs may reveal a wider range of associations with molecular variables; and (c) extrapolation of findings from non-ASD samples may 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 response to treatment and long-term clinical management.

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Fig. 1. Parent (ADHD) and teacher (generalized anxiety) ratings of symptom severity as a function of MAO-A genotype

Table 1
Descriptive Characteristics of Study Sample ($n = 43$)

Variable	3-repeat ($n = 12$)	4-repeat ($n = 31$)
Age (Mean/SD)	(7.8/2.1)	(7.9/2.6)
IQ (Mean/SD)	(82.3/24.8)	(81.7/24.3)
Caucasian (F/%)	12 (100)	31 (100)
Special education (F/%)	8 (67)	26 (84)
Medication (F/%)		
Current	3 (25)	10 (32)
Ever	7 (58)	14 (45)
SES (Mean/SD)	(44.0/13.2)	(42.7/10.3)
Single parent (F/%)	0 (0)	0 (0)
ASD Subtype (F/%)		
Autistic disorder	3 (25)	10 (32)
Asperger's disorder	3 (25)	10 (32)
PDD-NOS	6 (50)	11 (36)

Note: SES = socioeconomic status assessed with Hollingshead's⁵¹ index of occupational and educational social status; scores range from 24 (unskilled laborers) to 66 (major business and professionals)