Brief Report

A Preliminary Analysis of Interactions Between Genotype, Retrospective ADHD Symptoms, and Initial Reactions to Smoking in a Sample of Young Adults

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Abstract

Introduction: Initial reactions to cigarettes predict later regular smoking. Symptoms of attention deficit hyperactivity disorder (ADHD) have also been shown to increase smoking risk and may moderate the relationship between genotype and smoking. We conducted an exploratory study to assess whether ADHD symptoms interact with genetic variation to predict self-reported initial reactions to smoking.

Methods: Participants were a subsample of 1,900 unrelated individuals with genotype data drawn from the National Longitudinal Study of Adolescent Health (Add Health), a nationally representative sample of adolescents followed from 1995 to 2002. Linear regression was used to examine relationships among self-reported ADHD symptoms, genotype, and self-reported initial reactions to cigarettes (index scores reflecting pleasant and unpleasant reactions).

Results: Polymorphisms in the *DRD2* gene, *SLC6A4* gene, and among males, the *MAOA* gene interacted with retrospective reports of ADHD symptoms in predicting *pleasant* initial reaction to cigarettes. Polymorphisms in the *CYP2A6* gene and, among females, the *MAOA* gene interacted with retrospective reports of ADHD symptoms in predicting *unpleasant* initial reaction to cigarettes. No main effect for any of these polymorphisms was observed nor were any interactions with *DRD4* and *DAT* genes.

Conclusions: These findings suggest that genotypes associated with monoamine neurotransmission interact with ADHD

symptoms to influence initial reactions to cigarette smoking. Given that an initial pleasant reaction to cigarettes increases risk for lifetime smoking, these results add to a growing body of literature that suggests that ADHD symptoms increase risk for smoking and should be accounted for in genetic studies of smoking.

Introduction

Substantial research supports the heritability of smoking onset and dependence (Vink, Willemsen, & Boomsma, 2005), but the specific genetic pathways that confer risk have yet to be identified. Genetic factors putatively linked to neurotransmission of dopamine and serotonin may influence sensitivity to nicotine (e.g., Marks, Stitzel, & Collins, 1989; Perkins et al., 2008), and there is evidence that reactions to initial smoking experiences predict later regular smoking (Chen et al., 2003; DiFranza et al., 2004; O'Connor et al., 2005; Pomerleau, Pomerleau, & Namenek, 1998; Riedel et al., 2003), suggesting that specific genes may influence the onset of nicotine dependence by influencing initial responses to smoking.

Symptoms of attention deficit hyperactivity disorder (ADHD) represent another risk factor for smoking. Individuals with ADHD are significantly more likely to smoke and start smoking earlier compared with those without ADHD (Lambert & Hartsough, 1998; Milberger et al., 1997; Molina & Pelham, 2003; Pomerleau et al., 1995). Candidate gene studies have identified overlap among genetic markers associated with both ADHD and smoking phenotypes (e.g., *DRD2*, *DRD4*, *DAT1*, *CHRNA4*), suggesting that several common neurobiological mechanisms

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may give rise to this comorbidity (McClernon & Kollins, 2008). Thus, it is possible that certain genotypes, in the presence of ADHD symptoms, work together to enhance risk for smoking.

In a previous study, we assessed relationships among retrospectively reported ADHD symptoms, genotype, and risk for lifetime regular smoking in the same sample used in the current study (McClernon & Kollins, 2008; McClernon et al., 2008). Carriers of the *DRD2* Taq1 A2/A2 genotype with six or more hyperactivity-impulsivity symptoms were almost twice as likely to have a history of smoking as individuals carrying one or two copies of the A1 allele. Significant Genotype $\times$ ADHD Symptom interactions were also observed for polymorphisms in the *MAOA* and *DRD4* genes. This study was the first evidence of ADHD symptom by genotype interactions as predictors of any smoking outcome and suggested that putative smoking genotypes may interact with ADHD symptoms to increase risk for lifetime smoking. These interactions between genotype, ADHD, and lifetime risk for smoking, in combination with the previously identified link between initial reactions to cigarettes and risk for lifetime smoking, suggest that genetic factors may interact with ADHD symptoms to alter risk of nicotine dependence by influencing initial reactions to cigarettes.

Current Study

This study used a large epidemiological sample of young adults ($n = 1,900$) and evaluated ADHD symptoms as a potential moderator of the relationship between candidate gene variation and initial reactions to cigarettes. Given previously identified relationships between lifetime smoking, ADHD, and monoamine neurotransmission (e.g., McClernon et al., 2008), we hypothesized that candidate genes associated with monoamine regulation would interact with ADHD symptoms to influence initial reactions to cigarettes.

Methods

Participants

Data Source

Participants were a subsample from the National Longitudinal Study of Adolescent Health (Add Health), a large nationally representative study of adolescent health behaviors (<http://www.cpc.unc.edu/projects/addhealth>). Details regarding the design and data collection have been described elsewhere (Harris et al., 2003; Resnick et al., 1997).

Study Sample

The current study included the same sample ($n = 1900$) reported on in our previous paper (McClernon et al., 2008) and included respondents who (a) provided genetic data and (b) reported having smoked at least one cigarette in their lifetime. See Table 1 for demographic information on these individuals.

Genotyping

DNA collection, extraction, and genotyping methods have been described previously (for further details, see www.cpc.unc.edu/projects/addhealth). Polymorphisms in the following six genes were genotyped: the rs28363170 of dopamine transporter (*DAT*) gene, a 44-bp ins/del polymorphism (5HTTLPR) in the promoter region of the serotonin transporter (*SLC6A4*) gene, the rs1800497 of Taq1A polymorphism of the dopamine D2 receptor

Table 1. Demographics, Genotype, Attention Deficit Hyperactivity (ADHD) Symptoms, Conduct Disorder (CD) Symptoms, and Initial Reactions for Participants ($n = 1,900$)

	N ^a	%
Demographics		
Gender		
Male	921	48.5
Female	979	51.5
Ethnicity		
Caucasian	1,372	72.2
Non-Caucasian	504	26.5
Unknown	24	1.2
Mean age at Wave III	22.0	1.8 (SD)
Genotype		
<i>DAT</i>	1,829	
Any 9	695	38.0
10/10	1,134	62.0
<i>SLC6A4</i>	1,890	
s/s	374	19.8
s/l	872	46.1
l/l	644	34.1
<i>DRD2</i>	1,890	
Any A1	862	45.6
A2/A2	1,028	54.4
<i>DRD4</i>	1,892	
Any seven repeat	685	36.2
No seven repeat	1,207	63.8
<i>MAOA</i> (males)	913	
Inactive	381	41.7
Active	532	58.3
<i>MAOA</i> (females)	968	
Any Inactive	589	60.9
Active	379	39.1
<i>CYP2A6</i>	1,888	
Inactive	1,800	95.3
Active	88	4.7
ADHD symptoms	1,885	
>6 IN	76	4.0
>6 HI	93	4.9
Mean CD symptoms	1.37	1.80 (SD)
Pleasant initial reactions	2.48	2.36 (SD)
Unpleasant initial reactions	3.57	3.33 (SD)

Note. Values are numbers of subjects with percentages, except where means with SDs are noted. *CYP2A6* = the rs1801272 of the cytochrome P-450-A6 gene; *DAT* = the rs28363170 of dopamine transporter gene; *DRD2* = the rs1800497 of Taq1A polymorphism of the dopamine D2 receptor gene; *DRD4* = a 48-bp VNTR polymorphism of the dopamine D4 receptor gene; *MAOA* = a 30-bp VNTR in the promoter of the monoamine oxidase A gene; *SLC6A4* = a 44-bp ins/del polymorphism (5HTTLPR) in the promoter of the serotonin transporter gene; HI = hyperactive-impulsive; IN = inattentive.

^aNs vary slightly for each gene due to missing genotype information on some individuals.

(*DRD2*) gene, a 48-bp VNTR polymorphism of the dopamine D4 receptor (*DRD4*) gene, a 30-bp VNTR in the promoter of the monoamine oxidase A (*MAOA*) gene, and the rs1801272 of the cytochrome P-450-A6 (*CYP2A6*) gene.

Measures

Initial Reactions to Smoking

In Wave III of Add Health, participants were asked to retrospectively report on a 4-point scale of intensity (0 = *none*, 1 = *slight*, 2 = *moderate*, 3 = *intense*) the extent to which they experienced nine sensations during their first smoking experiences. Summary scores from these nine items create three scales (Hu, Davies, & Kandel, 2006; Pomerleau et al., 1998): (a) dizziness; (b) pleasant symptoms (pleasant sensations, relaxation, pleasurable rush, or buzz); (c) unpleasant symptoms (unpleasant sensations, nausea, coughing, difficulty inhaling, and heart pounding). Consistent with prior studies (Hu et al., 2006), these scales were grouped into pleasant (Cronbach's $\alpha = .78$) and unpleasant (Cronbach's $\alpha = .79$) initial reactions index scores for the analysis.

ADHD Symptoms

Participants retrospectively reported on *DSM-IV* ADHD symptoms in childhood (between 5 and 12 years) using a 4-point scale: *never or rarely*, *sometimes*, *often*, or *very often*. One *DSM-IV* impulsivity symptom ("often interrupts or intrudes on others") was not included in the retrospective ADHD section. Thus, our analyses included responses to nine inattentive (IN) and eight hyperactive-impulsive (HI) symptoms. A symptom was considered present if it was experienced often or very often (Murphy & Barkley, 1996). For our primary analyses, individuals were classified into one of two groups for each symptom domain based on the number of symptoms reported at a level of "often" or "very often". The six-symptom cutoff was chosen to be consistent with *DSM-IV* ADHD criteria requiring the presence of six or more symptoms from either the IN or the HI symptom domains.

Data Analyses

Statistical analyses were conducted using SAS-callable SUDAAN (version 8.0) software. SUDAAN allows for control of survey design effects of individuals clustered in a sampling unit of school and stratification of geographic region. Linear regressions were used to determine whether candidate genotypes predicted the pleasant or unpleasant initial reaction index scores. The specific genotypes were grouped for analysis according to the extant literature and are listed in Supplementary Table 1 (Hu et al., 2006; Munafo et al., 2004; Todd et al., 2005). Separate models were evaluated for each polymorphism using the Taylor Linearization method. The models were constructed to include main effects of the polymorphism, ADHD symptoms (IN or HI), and the interaction between polymorphisms and ADHD symptoms in predicting both pleasant and unpleasant initial reactions. Age, race, parental education level, and the presence or absence of CD were included as covariates.

Results

Results for all models are listed in Supplementary Table 1. No main effects were observed for any of the genotypes predicting either *pleasant* or *unpleasant* initial reactions. The following Genotype $\times$ ADHD Symptom interactions were found:

DRD2

We observed a significant Taq1A *DRD2* $\times$ HI interaction predicting pleasant initial reactions ($p = .03$), whereby, among

those individuals who had at least six HI symptoms, those who were homozygous for the A2 allele reported significantly higher initial *pleasant* reactions to cigarettes (predicted marginal means for those with at least six HI symptoms: any A1 = 1.81 vs. A2/A2 = 3.16, $p = .01$).

MAOA

For the *MAOA* 30-bp VNTR polymorphism, males and females were analyzed independently because this gene is located on the X chromosome. In males, we found a significant *MAOA* $\times$ IN interaction ($p = .01$). Among males who had at least six IN symptoms, we found higher *pleasant* reactions among those who were hemizygous for the active form of the gene (predicted marginals for those with at least six IN symptoms: inactive variant = 1.5 vs. active variant = 3.1, $p = .02$). In females, we found a significant *MAOA* $\times$ IN interaction ($p = .004$). Among females who had at least six IN symptoms, the presence of the homozygous active genotype predicted increased *unpleasant* reactions compared with those whose genotype included at least one copy of the inactive form of the gene (predicted marginals for those with at least six IN symptoms: one or more inactive = 1.57 vs. homozygous active = 6.12, $p = .004$).

SLC6A4

With regard to the *SLC6A4* 44-bp ins/del, we found a significant *SLC6A4* $\times$ HI interaction predicting pleasant initial reactions ($p = .02$). Among those individuals who had at least six HI symptoms, the presence of the s/s genotype was associated with higher initial *pleasant* reactions to cigarettes (predicted marginals for those with at least six HI symptoms: s/s = 4.09 vs. s/l = 1.87 vs. l/l = 2.79, $p = .02$).

CYP2A6

With regard to the rs1801272 polymorphism of *CYP2A6*, we found the following interactions. Among those individuals who had at least six IN symptoms, the presence of a 1/2 genotype was associated with fewer initial *unpleasant* reactions to cigarettes (predicted marginals for those with at least six IN symptoms: 1/2 = 1.77 vs. 1/1 = 3.35, $p = .05$). Similarly, among those individuals who had at least six HI symptoms, the presence of a 1/2 genotype was associated with fewer initial *unpleasant* reactions to cigarettes (predicted marginals for those with at least six HI symptoms: 1/2 = 2.11 vs. 1/1 = 3.57, $p = .02$).

To further validate our results, we repeated our analyses employing the Jackknife bootstrapping method in SUDAAN. The p values were slightly smaller using the Jackknife estimation method, but the interaction effects remained statistically significant (see Supplementary Table 1).

Discussion

The present study assessed relationships among retrospectively reported ADHD symptoms, genotype, and initial reactions to smoking in a U.S. sample of young adults. Significant Genotype $\times$ ADHD Symptom interactions were observed for variants of the *DRD2*, *MAOA*, *SLC6A4*, and *CYP2A6* genes. This is the first evidence of ADHD symptom by genotype interactions as predictors of initial reactions to cigarettes, which are thought to predict the likelihood of future smoking.

The present study extends our previous finding of significant relationships between *DRD2* and *MAOA* genotypes, self-reported ADHD symptoms, and lifetime smoking (McClernon et al., 2008) by suggesting that these same genetic variants influence initial reactions to cigarettes in the presence of ADHD symptoms. Thus, it may be that one of the mechanisms underlying the association among ADHD symptoms, genotype, and regular smoking is the effect that the Gene $\times$ Symptom interaction has on initial reactions to smoking experiences.

Limitations

The present study is limited by factors related to the measurement of the dependent and independent variables. First, initial reactions to smoking were assessed retrospectively. While this is a limitation commonly faced by studies of initial reactions to cigarettes, studies examining initial reactions more proximal to actual early smoking experiences would be beneficial. Second, ADHD symptoms were assessed using retrospective self-report. Although this approach to characterizing childhood ADHD symptoms has been shown to be both reliable and valid, it is, nevertheless, not ideal (Kollins, McClernon, & Fuemmeler, 2005; Ward, Wender, & Reimherr, 1993; Zucker et al., 2002). Third, the genetic data available for analysis were limited as only six polymorphisms across six candidate genes were available for analysis. Moreover, the frequency of some of the genetic variants in the current study (e.g., variants of the *MAOA* and *CYP2A6* genes) is very low and, when considered along with the ADHD symptom variables, produced very low cell counts. Fourth, a large number of statistical tests were conducted in the present analyses, which may have inflated the risk of Type I error. However, the risk of Type I error was likely mitigated to a large degree by our theory-based approach and by the fact that the genes examined have been studied previously in the context of smoking or ADHD. Therefore, replication is needed to further substantiate these findings.

Conclusions

Despite these limitations, this study is strengthened by the fact that it is the first study to systematically examine the influence of genetic variation and ADHD symptoms on initial reactions to smoking. The associations found with initial reactions to cigarettes and interactions with specific genotypes (e.g., *DRD2*, *SLC6A4*, *CYP2A6*, and *MAOA*) and ADHD symptoms add to a growing body of literature examining Genotype $\times$ Trait interactions to predict smoking outcomes (Audrain-McGovern et al., 2004; Breslau et al., 1998; de Leon et al., 1995; Lerman et al., 2000). Taken together, these findings indicate that the relationship between genetic risk factors and smoking may be further qualified by psychiatric symptoms and personality traits that increase risk for smoking. The present study provides an important step toward identifying psychiatric and genetic determinants of smoking initiation and progression among adolescents, and additional work is needed to identify the neurobiological and molecular genetic mechanisms that underlie these unique associations.

Supplementary Material

Supplementary Table 1 can be found online at <http://www.ntr.oxfordjournals.org>

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Declaration of Interests

Redford Williams holds U.S. patent 7,371,522 on the use of the 5HTTLPR L allele as a genetic marker of increased risk of cardiovascular disease in persons exposed to chronic stress.

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