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Nicotinic receptor gene variants interact with attention deficient hyperactive disorder symptoms to predict smoking trajectories from early adolescence to adulthood

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Abstract

Objective—To examine the association of single nucleotide polymorphisms (SNPs) of the CHRNB3 (rs13280604) and CHRNA6 (rs892413) nicotinic acetylcholine receptor (nAChR) genes and symptoms of attention deficit hyperactivity disorder (ADHD) in predicting smoking patterns from early adolescence to adulthood.

Method—A longitudinal cohort of 1137 unrelated youths from the National Longitudinal Study of Adolescent Health provided responses to four surveys from Waves I to IV, and a genetic sample in Wave III. Growth mixture modeling was used to identify smoking patterns and to assess the effects of the two SNPs and ADHD symptoms on cigarette use over time.

Results—There were significant main effects of ADHD symptoms and CHRNA6 variants in predicting the number of cigarettes smoked and the pattern of use over time, respectively. There

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Contributors

The authors declare that each of them have materially participated in the research and/or the manuscript preparation. The first author conducted the statistical analyses and took the lead role in writing the first draft of the manuscript. Both second and fifth authors designed the study and made significant contributions to later drafts of the manuscript. The fifth author also conducted literature searches and provided summaries of previous research studies. The third author and the fourth author also contributed significantly to the interpretation of the results. All authors contributed to and have approved the final manuscript.

Conflict of interest

These disclosures do not represent potential conflicts of interest. Dr. Fuemmeler, Dr. Ashley-Koch, and Dr. Lee declare no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.addbeh.2013.06.013.

were no main effects of the CHRNB3 variants. However, a significant CHRNB3 variant × ADHD symptom interaction was observed, such that individuals with elevated ADHD symptoms and a particular CHRNB3 variant were at increased risk of cigarette use over time.

Conclusions—These findings demonstrate that a SNP in a nicotinic receptor gene may interact with ADHD symptoms to link with increased cigarette use across adolescence and young adulthood. Unique associations between specific variants and patterns of ADHD symptoms were identified which may be useful for targeting prevention efforts to individuals at greatest risk for cigarette smoking.

Keywords

nAChR SNPs; ADHD; Smoking development

1. Introduction

Variants of nicotinic-acetylcholine receptor (nAChR) complex genes have been widely studied as predictors of a range of smoking outcomes (Greenbaum & Lerer, 2009; Russo et al., 2011; Ware, van den Bree, & Munafo, 2011; Winterer et al., 2010; Zhang, Kranzler, Poling, & Gelernter, 2010). Eleven different nAChR subunit-encoding genes have been identified, including the CHRNB3 and CHRNA6 genes, both of which are located at chromosome 8p11.2. Results from genome wide association studies (GWAS) and candidate gene studies show that variations in the CHRNA6–CHRNB3 gene cluster are associated with likelihood and severity of nicotine dependence (Bierut et al., 2007), heavy smoking (Stevens et al., 2008), and initial subjective responses to smoking (Zeiger et al., 2008). However, these associations have not been well documented and replicated in studying trajectories of cigarette use over time.

A diagnosis of attention deficit hyperactivity disorder (ADHD) has also been shown to confer risk for a wide range of smoking related outcomes. Adults and adolescents with ADHD have higher rates of smoking than the general population and/or non-diagnosed controls (Milberger, Biederman, Faraone, Chen, & Jones, 1997; Molina & Pelham, 2003; Rohde, Kahler, Lewinsohn, & Brown, 2004). Further, individuals with ADHD who start smoking at an earlier age are more likely to progress to regular smoking following initial experimentation, experience more severe withdrawal symptoms following abstinence, and are more likely to have difficulty quitting smoking (Humfleet et al., 2005; McClernon et al., 2011). Moreover, ADHD symptoms, independent of a clinical diagnosis of ADHD, are also related to smoking related outcomes including lifetime smoking risk, progression from experimentation to regular use, severity of nicotine dependence, severity of smoking withdrawal symptoms, and smoking motivation (Kollins, McClernon, & Fuemmeler, 2005; Lerman et al., 2001; Tercyak, Lerman, & Audrain, 2002).

A genetic liability for ADHD has been well established (Li, Sham, Owen, & He, 2006), and there is some evidence to suggest that neuronal nAChR gene variation may be associated with ADHD risk, however, findings across studies are inconsistent. For example, some studies have reported a significant association between polymorphisms of the α-4 subunit gene (CHRNA4) and ADHD (Todd, Lobos, Sun, & Neuman, 2003; Wallis et al., 2009). However, others have failed to replicate this finding (Kent et al., 2001). Related phenotypes, such as attention, have also been shown to vary as a function of CHRNA4 variants (Winterer et al., 2007). To the best of our knowledge, little is known regarding how CHRNA6 and CHRNB3 confer risk for ADHD symptoms or related behavioral phenotypes. Variants in the CHRNA6 and CHRNB3 may be important to dopamine (DA) function and have been associated with rewarding aspects of nicotine (Zeiger et al., 2008). Gene ×

psychiatric symptom interactions have been reported previously as being important to predict smoking outcomes, including studies investigating nAChR and DA related genes (Audrain-McGovern, Lerman, Wileyto, Rodriguez, & Shields, 2004; Greenbaum et al., 2006; McClernon, Fuemmeler, Kollins, Kail, & Ashley-Koch, 2008). Given the central role of dopamine and the reward/motivational circuitry in the pathophysiology of ADHD (Volkow et al., 2009, 2011), we therefore sought to extend these findings by examining the interactions between ADHD symptoms and nAChR gene variants in determining cigarette smoking development.

Our previous work, using genetic data available at the time, has shown that genetic factors may moderate the relationship between self-reported ADHD symptoms and smoking outcomes among subsamples of Add Health cohort. McClernon et al. (2008) reported that variants of the dopamine D2 receptor gene (DRD2) and the monoamine oxidase-A (MAO-A) gene interacted with ADHD symptoms to predict risk for lifetime regular smoking in a subsample of young adults. Likewise, Bidwell et al. (2012) showed interactions between variants of DRD2, MAO-A, and SLC6A4 (serotonin transporter) genes and ADHD symptoms in predicting initial subjective responses to smoking. It is worth noting that in both studies, there were differences in the findings based on subdomains of ADHD symptoms. For example, only levels of Hyperactive–Impulsive symptoms interacted with DRD2 variants to predict regular smoking (McClernon et al., 2008); and only high levels of Inattention symptoms interacted with MAO-A variants to predict initial subjective responses to smoking (Bidwell et al., 2012). Owing to the findings that nAChR genes and ADHD symptoms have independently associated with smoking outcomes, the interaction of specific alleles of nAChR genes with ADHD symptoms is hypothesized. This is because both factors represent a vulnerability to smoking and the combination may further explain why some individuals who have ADHD symptoms may be at an even greater risk for addiction than others. The goal of the current study was to investigate similar interactions between ADHD symptoms and how nAChR genetic variation predicts smoking development from early adolescence into adulthood.

2. Method

2.1. Study sample

Subjects for this study were drawn from the National Longitudinal Study of Adolescent Health (Add Health), which includes 15,701 respondents who completed in-home surveys in 1995 and up to three additional times; 1996, 2001–2002, and 2008–2009 (Waves I–IV, respectfully). The design and data collection methods have been described in detail elsewhere (Harris et al., 2009; Resnick et al., 1997). At Wave III, subsamples of related and non-related individuals were asked to provide buccal cell samples for genetic analysis (n = 2574). In the current study, non-related participants and randomly selected participants from families with more than one child participating were chosen. Variants in the CHRNA6–CHRNB3 regions were recently released for public use by the Add Health study team and were used for analysis in this study. Overall, among these participants, 343 were missing sampling weights resulting in a total sample of 1137 non-related individuals that were used for analysis. The mean age of participants at Wave I was 16.13 (SD = 1.66). Missing data for variants, ADHD symptoms, smoking behaviors, demographic characteristics, and conduct problems resulted in variability in the total number of individuals available for each analysis.

2.2. Measures

2.2.1. Smoking status—Participants were asked whether they had ever smoked and the number of cigarettes smoked in the past 30 days using a computer aided survey instrument

(CASI) at all waves. Based on participants' responses, the average number of cigarettes smoked per day on the days smoked in the past 30 days was further quantified for each wave. Participants who had never smoked or who had not smoked during the past 30 days were included in the analysis as having smoked zero cigarettes in the past 30 days.

2.2.2. ADHD symptoms—At Wave III, participants reported on Diagnostic and Statistical Manual-IV (DSM-IV) ADHD symptoms experienced between the ages of 5 to 12 years. Responses were on a 4 point scale: 1) never or rarely; 2) sometimes; 3) often; or 4) very often. One of the Hyperactive–Impulsive ADHD symptoms, “Often interrupts or intrudes on others”, was not available in the dataset, and then only nine inattentive and eight hyperactive symptoms were available for analysis. A symptom was considered present if it was experienced “often” or “very often” and symptoms were grouped into the domains of either Hyperactive–Impulsive (HI) or Inattention (IN). This scoring approach is consistent with clinical convention and has been validated in other studies (Fuemmeler, Kollins, & McClernon, 2007; Murphy & Barkley, 1996). The reliability coefficients for the HI and IN symptoms for this analytic sample were .75 and .80 respectively, indicating an adequate internal consistency for each. ADHD symptoms in this sample also demonstrated convergent validity (Kollins et al., 2005; McClernon et al., 2008). The mean of HI and IN symptoms of the studied participants was 1.59 (*SD* = 1.82) and 1.17 (*SD* = 1.85), respectively. Because conduct problems (CP) has been shown in previous studies to be interplayed with ADHD and contributed to the risk of substance use, therefore, besides demographic variables, the present study also controlled for CP to increase the internal validity of our results.

2.2.3. Genotyping procedures—Buccal tissue samples were collected from the participants and DNA was extracted using a modification of procedures described previously (Freeman et al., 1997; Lench, Stanier, &Williamson, 1988; Meulenbelt, Droog, Trommelen, Boomsma, & Slagboom, 1995; Spitz et al., 1998). Genomic DNA was isolated and subsequently preamplified using the whole genome Primer Extension Preamplification (PEP) method (Zhang et al., 1992) TaqMan assays for allelic discrimination were used to determine SNP genotypes, using ABI PRISM 700 and 7900 instruments (for further details, see www.cpc.unc.edu/projects/addhealth). Initially, 2 SNPs from both the CHRNA6 and CHRNB3 genes were genotyped, however, SNP rs13280604was in strong linkage disequilibrium (LD) with rs4950 in the CHRNB3 gene and SNP rs892413 was in strong LD with rs2304297 in the CHRNA6 gene. Because there was more missing data for rs4950 in CHRNB3 and rs2304297 in CHRNA6, we focused our analyses on rs13280604 (A/G) and rs892413 (A/C). Prior to conducting the main analyses, each SNP was checked for Hardy–Weinberg equilibrium (HWE) within ethnic groups using the Chi-square test with Yate's continuity correction and Haldane's Exact test in R (Graffelman & Camarena, 2008).

2.3. Data analysis

Statistical analyses were conducted using *Mplus* 6.12 (Muthén & Muthén, 1998–2011). Survey weights were incorporated in analyses to compensate for differences in selection probabilities of cases within sampling units, differential rates of non-response, and chance fluctuations of the sample from the population as a whole. To evaluate smoking over the course of adolescent development, the data was restructured by age instead of wave (Duncan, Duncan, Strycker, & Chaumeton, 2007). Zero-inflated Poisson (ZIP) latent growth curve modeling was used to examine the smoking outcome, which contained a majority of non-users. ZIP growth modeling provides simultaneous estimation for two analytic features of smoking behaviors: the binary contrast between non-users and users, and the count construct indicating the number of cigarettes smoked among users (Liu & Powers, 2007).

Separate models were constructed for both SNP's (CHRNB3 and CHRNA6) and each ADHD symptom domain (IN or HI) to examine the main effects of the SNP and symptom domain while controlling for sex, race, parental education and history of conduct problems. Subsequently, the interaction between ADHD symptom domain and SNP were added. Next, SNP × ADHD interactions were added to these models. Similar to previous studies of this sample (McClernon et al., 2008), sex, race, parental education, and the presence of conduct problems (CP) were again included as covariates in the analyses (Holmbeck, 2002). For significant SNP × ADHD symptom domain interactions, post hoc probing was conducted. To do this, smoking trajectories were regressed on the SNP at high (defined as 1 *SD* above the mean) and low levels (defined as 1 *SD* below the mean) of the ADHD symptom domain (HI or IN) while controlling for the previously mentioned covariates. Significant differences in the allele frequencies between non-Hispanic White and African Americans have been documented in previous studies of the SNPs of interest and were present in these data (Hoft et al., 2009; Zeiger et al., 2008). Thus, all analyses were conducted on the sample as a whole while controlling for race. Then a series of supplementary analyses was conducted on a subsample restricted to non-Hispanic White participants only.

3. Results

Demographically, participants were 59% non-Hispanic White, 18% non-Hispanic Black, 14% Hispanic, and 9.4% Other. Females represented 54% of the sample. Fifty percent of participants had parents who completed high school, 20% had parents who received a college degree or higher, 16% had parents without a high school diploma, and 14% had parents who completed some college. For all ethnic groups except African Americans, the most frequently observed allele combination for SNP rs13280604 was AA (58.4%), while GG (9.0%) was the least frequently observed combination. Among African American participants, AA (57.1%) was the most frequently observed combination and CC was the least frequently observed combination in SNP rs892413. Further details are presented in Table 1. Within ethnic groups, Chi-square tests showed that both SNPs were within expectations for Hardy–Weinberg equilibrium.

For the binary trajectory, a significant negative linear slope (slope $b = -1.98$, $SE = 0.68$) indicated that the prevalence of abstinence from smoking (non-use) decreased and a significant positive quadratic (quadratic $b = 0.88$) indicated a deceleration in this decrease over time. Among those who did smoke (i.e., the count trajectory), the intercept (at age 13) was $b = -1.15$. A significant positive slope indicated that the number of cigarettes smoked increased with age (slope $b = 1.49$) while the quadratic (quadratic $b = -0.57$) suggested a deceleration in this rate over time.

3.1. CHRNB3 (RS13280604)

The main effects and interactions of SNP rs13280604 and ADHD symptoms in predicting smoking trajectories are presented in Table 2. Model 1 showed that no main effects of rs13280604 variants were observed. HI symptoms were related to a greater increase in the number of cigarettes smoked after age 13 (slope $b = 0.48$, $p = 0.001$) and a faster deceleration in this rate over time (quadratic $b = -0.27$, $p < 0.001$). IN symptoms were related to a slower increase in the number of cigarettes smoked after age 13 ($b = -0.40$, $p = 0.005$), but a slower deceleration in this rate over time ($b = 0.22$, $p = 0.003$).

Significant interaction effects were observed between rs13280604 variants and HI symptoms in predicting the number of cigarettes smoked (Model 2). Post hoc results (Table 3) showed that within the group of individuals with the AA variant, individuals with high levels of HI symptoms smoked more cigarettes at age 13 than those with low levels of HI symptoms, 95% CIs (−0.79, 1.21) and (−2.21, −0.84), respectively. However, differences

between groups (AA, AG, or GG) in the number of cigarettes smoked were only seen among those with low HI symptoms. Specifically, individuals with the AA variant had a significantly lower number of cigarettes smoked at age 13 [intercept $b = -1.54$, 95% CI (−2.24, −0.84)], a more rapid increase in the number of cigarettes smoked after age 13 [slope $b = 2.44$, 95% CI (0.35, 4.52)], and a greater deceleration in this rate over time [quadratic $b = -1.30$, 95% CI (−2.34, −0.26)] compared to those with the GG variant.

Significant interactions were also observed between rs13280604 variants and IN symptoms in predicting the probability of cigarette use and number of cigarettes smoked. Post hoc tests indicated that regardless of IN symptom level, a crossover pattern of smoking trajectories was identified. None of these contrasts, however, reached statistical significance as indicated by the overlapping 95% CIs. Additionally, the probability of cigarette use over time between high and low levels of IN symptoms for individuals with the same variant did not differ significantly.

With respect to the number of cigarettes smoked, the post hoc probe revealed that at high levels of IN symptoms, individuals with the AA or AG variants smoked lower numbers of cigarettes at age 13 [AA intercept $b = -1.69$, 95% CI (−2.90, −0.48); AG intercept $b = -0.89$, 95% CI (−1.83, 0.05)], demonstrated greater increases in the number of cigarettes smoked since age 13 [AA slope $b = 3.58$, 95% CI (0.69, 6.47); AG slope $b = 2.93$, 95% CI (0.33, 5.53)] and more rapid decelerations in this increase over time [AA quadratic $b = -1.69$, 95% CI (−2.92, −0.46); AG quadratic $b = -1.31$, 95% CI (−2.58, −0.05)] compared to those with the GG variant. At low levels of IN symptoms, individuals with the AG variant smoked a greater number of cigarettes at age 13 [intercept $b = 1.28$, 95% CI (0.55, 2.01)] and demonstrated a more gradual increase in the number of cigarettes smoked since age 13 [slope $b = -1.87$, 95% CI (−3.63, −0.12)] compared to those with the GG variant.

Comparing high and low in IN symptoms among individuals with the AA variant, those with high IN symptoms had a more rapid increase in the number of cigarettes used with this rate decelerating more rapidly over time [95% CIs, (0.69, 6.47), (−2.92, −0.46)] than their counterparts with low IN symptoms [95% CIs, (−2.93, 0.21), (−0.38, 1.15)]. Within the AG variant group, high levels of IN symptoms were associated with fewer cigarettes smoked at age 13, but a more rapid increase in the number smoked since age 13 [95% CIs, (−1.83, 0.05), (0.33, 5.53)] than their counterparts with low levels of symptoms [95% CIs, (0.55, 2.01), (−3.63, −0.12)].

When restricting to the non-Hispanic White sample, a similar pattern of the main effects of SNP rs13280604 and ADHD symptoms emerged. With regard to ADHD symptoms at high and low levels, the directions of the associations between SNPs and smoking trajectories were similar to those identified in the full sample (see Supplementary Tables). Although the directions of the associations among non-Hispanic White participants matched those of the full sample, a few of the associations did not reach the same levels of statistical significance. These differences can likely be attributed to both differential sample size and variability in the between samples.

3.2. CHRNA6 (RS892413)

Models 3 and 4 in Table 2 display the results of regressing smoking trajectories on ADHD symptoms and SNP rs892413 and their interaction terms. Model 3 shows that the main effects of HI and IN were significant predictors of the number of cigarettes smoked. There were also significant main effects of the AA (vs. CC) variant in predicting the number of cigarettes smoked. Specifically, individuals with the AA variant smoked fewer cigarettes at age 13 (intercept $b = -1.12$, $p < 0.001$), more gradually increased the number of cigarettes smoked since age 13 (intercept $b = 1.24$, $p = 0.066$) and this rate decelerated more rapidly

over time (quadratic $b = -0.79$, $p = 0.014$). There were no main effects of the AC variant on smoking outcomes (see Model 4). Additionally, no significant rs892413 × ADHD symptom interactions predicting cigarette use or the number of cigarettes smoked were identified.

In the non-Hispanic White subsample (see Supplementary Table 2), significant AA × HI and AC × HI interactions on the number of cigarette smoked were observed at the intercept (age 13). Post hoc tests suggested that at both high and low levels of HI symptoms, individuals with the AA [95% CIs (−1.40, −0.21), (−2.57, −1.13)] or AC variants [95% CIs (−1.47,−0.41), (−1.73,−0.28)] had lower levels of cigarette use at age 13 compared to those with the CC variant [95% CIs (0.30, 4.80), (0.13, 4.03)]. Nevertheless, within individuals with the same variant, association with the number of cigarette smoked did not differ significantly between high and low levels of HI symptoms.

4. Discussion

The present study examined the relationships among ADHD symptoms, nAChR complex genes, and trajectories of smoking behavior from age 13 to 32. A benefit of using a growth modeling approach is that it allowed for an analysis of how ADHD symptoms and CHRNA6–CHRNB3 gene variants contributed independently and in combination with patterns of use vs. non-use, as well as the number of cigarettes smoked over time. The results suggest that variability in nAChR SNPs, in combination with ADHD symptoms, can predict risk of cigarette use over time. While previous studies were limited to reporting interactions of genes and psychiatric symptoms (Audrain-McGovern et al., 2004; Lerman et al., 2000) to predict smoking outcomes, the current findings are the first to demonstrate the role of CHRNA6–CHRNB3 receptor complex as a moderator of smoking related outcomes in the context of ADHD symptoms.

There were significant CHRNB3 genotype × ADHD symptom interactions influencing the trajectory of the number of cigarettes used. Our findings highlight that the association between the CHRNB3 genotype and smoking is influenced by the presence or absence of ADHD symptom severity. Specifically, the presence of the AA variant and high IN symptoms was associated with the highest number of cigarettes smoked over early adolescent development, followed by AG and high IN symptoms. Those with high IN symptoms and the GG variant were at the lowest risk of smoking. The observed interaction effect helps to reveal that not all individuals who were high in ADHD symptoms also reported problems with smoking. Researchers have suggested that certain aspects of neurocognitive functioning, such as sustained attention (Greenbaum & Lerer, 2009; Rigbi et al., 2008; Russo et al., 2011; Ware et al., 2011; Winterer et al., 2010; Zhang et al., 2010), could be a potential mechanism for both smoking vulnerability and components of the ADHD phenotype. Also, variation in subunits of the nAChRs, including rs13280604, plays a role in dopamine modulation which may affect ADHD symptoms and reinforce cigarette usage (Zeiger et al., 2008). Therefore, there may be shared biological pathways which may help explain why individuals with ADHD symptoms, who also differ genetically at this SNP, may be different than those with minimal ADHD symptoms. Mechanistic studies will be needed to further characterize these synergies and better explain the heterogeneous response to smoking/nicotine among individuals with ADHD symptoms.

The present results also show variation in the trajectories of the number of cigarettes used in individuals with variants of the CHRNA6 rs892413 SNP. Others studies have not observed associations between SNP rs892413 and smoking outcomes, such as initial reaction to smoking (Zeiger et al., 2008) and likelihood of being a current frequent smoker (Hoft et al., 2009). One possible explanation for our unique findings is that, unlike previous studies, our

study assessed smoking behaviors over a 20 year period allowing for a more comprehensive evaluation of the developmental smoking phenotype.

Despite the many benefits afforded by our approach, there are several limitations to this study. ADHD symptoms were measured using a retrospective self-report. Although previous studies have shown this to be a reliable method of assessing ADHD symptoms (Kollins et al., 2005), a more comprehensive and prospective approach to assess ADHD symptoms would have been ideal. Likewise, smoking behavior was also assessed only on the basis of self-report. Prospective measures with biochemical verification would have increased confidence in the validity of these outcomes; however, this approach is often not feasible in large epidemiologic longitudinal studies addressing multiple risk factors and outcomes. The sample size, especially for the non-Hispanic White subsample, for the available genetic analyses was limited, resulting in low cell counts for several of the minor alleles × symptom categories and thus stratified analyses of minority groups could not be performed reliably. Replication with larger and more diverse samples is needed to further substantiate these findings. Moreover, these findings should be interpreted with the caveat that a number of statistical comparisons were made, possibly inflating the risk for type I error. Spurious results are a hazard in psychiatric genetics research involving gene-by-environment (G × E) interactions and thus future independent validation studies are needed (Duncan & Keller, 2011). Finally, given the nature of both the sample and data, we only had access to data on the CHRNA6 and CHRNB3 gene clusters that were part of the most recent release in the Add Health dataset. As such, more studies are needed to address other nAChR genes, such as the CHRNA5–CHRNA3 cluster, and their association with ADHD and smoking.

While it is necessary to address the limitations, it is also essential to highlight the importance of the present study's novel identifications of the interactions between ADHD symptoms and variations in nicotinic receptor genes in predicting trajectories of smoking behavior. These not only suggest that the inclusion of the interactions might enhance the understanding of factors underlying smoking initiation and development over time but may also help guide future prevention and intervention efforts. One potential avenue for improving prevention efforts would be to aim resources at identifying high-risk adolescents based on the observed severity of ADHD symptoms. Specific genetic markers in the context of ADHD symptom severity may aid the development of more effective interventions by tailoring treatment methods to an individual's geno- and phenotypic combination (Lerman et al., 2003). Additional research is needed to further clarify the underlying genetic, neurobiological, and behavioral mechanisms responsible for the observed associations. Human laboratory studies examining the effects of genetic variation and psychiatric symptoms in moderating specific smoking outcomes including nicotine reactivity, smoking reinforcement, withdrawal and/or cessation among current smokers, and smoking development in nicotine naïve individuals should be pursued with the goal of translating the current findings into clinically relevant approaches for prevention and treatment of smoking.

5. Conclusions

These findings demonstrate that a SNP in a nicotinic receptor gene may interact with ADHD symptoms to link with increased cigarette use across adolescence and young adulthood. Unique associations between specific variants and patterns of ADHD symptoms were identified which may be useful for targeting prevention efforts to individuals at greatest risk for cigarette smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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HIGHLIGHTS

- Associations between nAChR SNPs, ADHD symptoms, and smoking patterns were examined.
- Growth modeling used to identify smoking patterns based on SNP and ADHD symptoms.
- ADHD symptom severity predicted the number of cigarettes smoked.
- Certain CHRNA6 variants predicted pattern of cigarette use over time.
- CHRNB3 variant × ADHD symptom interaction increased risk of cigarette use over time.

Table 1

Descriptive statistics of SNPs stratified by ethnic group.

	non-Hispanic White		non-Hispanic Black		Hispanic		Other	
	n	%	*n*	%	*n*	%	*n*	%
rs13280604								
AA	361	59.7	18	11.4	67	46.6	60	60.6
AG	193	32.5	67	37.6	62	34.0	27	32.3
GG	40	7.8	89	51.0	16	19.4	6	7.1
rs892413								
AA	389	60.5	30	19.1	67	43.0	57	44.7
AC	208	34.9	75	40.6	68	37.9	39	48.9
CC	34	4.6	84	40.3	19	19.1	6	6.4

Note. Percentage was adjusted for the complex survey design.

Table 2

Smoking trajectories regressed on ADHD symptoms, rs13280604/rs892413, and their interaction terms.

	Non-use vs. use						*Number of smoked*					
	Intercept		**Slope**		**Quad**		**Intercept**		**Slope**		**Quad**	
Model	***Est.***	***SE***	***Est.***	***SE***	***Est.***	***SE***	***Est.***	***SE***	***Est.***	***SE***	***Est.***	***SE***
# 1												
Intercept	*NA*		0.77	6.63	−1.52	3.36	−0.69	1.14	2.16	2.40	−0.70	1.20
HI	−0.10	0.22	0.34	0.74	−0.23	0.39	−0.07	0.07	0.48**	0.15	−0.27***	0.07
IN	0.02	0.18	−0.43	0.73	0.25	0.39	0.11	0.06	−0.40**	0.15	0.22**	0.07
AA	1.48	1.39	−3.16	4.41	1.89	2.09	−0.75	0.39	0.61	0.82	−0.39	0.33
AG	2.06	1.75	−4.31	4.49	2.36	2.02	0.06	0.42	−0.05	0.96	−0.03	0.45
# 2												
Intercept	*NA*		−0.97	6.69	−1.03	3.26	−1.36	1.25	2.03*	2.25	−0.54	1.03
AA * HI	0.24	0.49	−0.33	1.42	−0.50	0.74	0.51*	0.20	−0.73*	0.37	0.36*	0.18
AG * HI	0.76	0.50	−1.93	1.61	0.45	0.87	0.47*	0.19	−0.56	0.35	0.27	0.18
AA * IN	−1.36*	0.62	3.86*	1.95	−1.29	0.99	−0.58**	0.20	1.34**	0.51	−0.56*	0.23
AG * IN	−1.80**	0.68	5.26**	2.03	−2.20*	1.06	−0.59**	0.16	1.30**	0.47	−0.54*	0.24
# 3												
Intercept	*NA*		−4.75	5.14	1.74	2.70	−1.90	1.46	2.92	2.21	−0.99	1.12
HI	−0.10	0.19	−0.07	0.53	−0.06	0.29	−0.10	0.08	0.50**	0.17	−0.28***	0.07
IN	−0.06	0.13	−0.00	0.49	0.05	0.29	0.25***	0.05	−0.32**	0.11	0.15**	0.05
AA	−0.03	0.78	3.21	3.52	−1.98	1.82	−1.12***	0.29	1.24	0.68	−0.79*	0.32
AC	−0.54	0.82	4.84	3.17	−2.67	1.63	−0.07	0.34	0.72	0.72	−0.51	0.39
# 4												
Intercept	*NA*		−6.95	4.65	2.80*	2.51	−0.88*	1.32	2.36	2.25	−0.78	1.11
AA * HI	−1.45	1.10	4.94	3.51	−2.45	1.81	0.18	0.18	0.26	0.38	−0.08	0.20
AC * HI	−0.10	1.18	1.17	3.59	−0.52	1.86	0.12	0.16	0.29	0.41	0.07	0.24
AA * IN	0.72	0.67	−3.17	2.09	1.70	1.10	−0.18	0.32	−0.24	0.53	0.05	0.20
AC * IN	−0.20	0.79	−0.38	2.27	0.14	1.21	−0.41	0.27	−0.14	0.44	−0.06	0.17

Note. Models 1 and 2 were results for SNP rs13280604 and comparison group was GG variant (n = 871) whereas Models 3 and 4 (n = 935) were for SNP rs892413 and the comparison group was CC variant. HI = Hyperactive–Impulsive symptoms. IN = Inattentive symptoms.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 3

Post hoc probing of interactions of rs13280604 variants at high and low levels of ADHD symptoms (n = 871).

	Non-use vs. use						*Number of smoked*					
	Intercept		**Slope**		**Quad**		**Intercept**		**Slope**		**Quad**	
Condition	***b***	**95% CI**	***b***	**95% CI**	***b***	**95% CI**	***b***	**95% CI**	***b***	**95% CI**	***b***	**95% CI**
HI-High												
Intercept	NA		1.36	−11.25, 13.98	−1.27	−7.40, 4.87	−1.78	−4.06, 0.50	3.89	−0.64, 8.41	−1.51	−3.68, 0.66
AA	1.99	−1.00, 4.97	−2.90	−10.12, 4.33	0.96	−3.21, 0.67	0.21	−0.79, 1.21	−0.08	−1.93, 1.78	−0.74	−0.82, 0.68
AG	3.42*	0.30, 6.53	−6.74*	−13.42, −0.05	3.08	−4.27, −012	0.90	−0.03, 1.84	−0.39	−2.04, 1.26	0.10	−0.62, 0.82
HI-Low												
Intercept	NA		−3.29	−17.66, 11.09	−0.83	−8.03, 6.37	−0.65	−3.11, 1.81	0.01	−4.41, 4.42	0.50	−1.52, 2.52
AA	1.16	−1.45, 3.78	−1.82	−11.51, 7.87	−1.29	−1.90, 7.54	−1.54***	−2.24, −0.84	2.44*	0.35, 4.52	−1.30*	−2.34, −0.26
AG	0.69	−2.77, 4.15	0.20	−10.87, 11.26	−2.20	−3.74, 6.70	−0.65	−1.39, 0.08	1.55	−0.89, 3.98	−0.81	−2.03, 0.42
IN-High												
Intercept	NA		−9.68	−23.81, 4.45	2.41	−4.36, 9.19	−0.07	−2.01, 1.87	−1.03	−5.34, 3.28	0.83	−1.18, 2.84
AA	−0.91	−3.85, 2.03	4.71	−6.04, 15.45	−10.47	−5.22, 4.28	−1.69**	−2.90, −0.48	3.58*	0.69, 6.47	−1.69**	−2.92, −0.46
AG	−1.26	−4.90, 2.38	6.40	−4.31, 17.12	−1.76	−6.58, 3.05	−0.89	−1.83, 0.05	2.93*	0.33, 5.53	−1.31*	−2.58, −0.05
IN-Low												
Intercept	NA		7.85	−5.65, 21.34	−4.54	−11.68, 2.59	−2.63**	−4.48, −0.79	5.12*	0.81, 9.44	−1.93	−4.12, 0.26
AA	4.08*	0.77, 7.40	−9.53*	−18.32, −0.74	4.27	−0.59, 9.13	0.39	−0.49, 1.26	−1.36	−2.93, 0.21	0.39	−0.38, 1.15
AG	5.39**	1.66, 9.11	−12.97**	−22.32, −3.62	6.32*	1.18, 11.47	1.28**	0.55, 2.01	−1.87*	−3.63, −0.12	0.66	−2.67, 1.58

* $p < .05$.

** $p < .01$.

*** $p < .001$.