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Cigarette Experimentation in Mexican Origin Youth: Psychosocial and Genetic Determinants

Anna V. Wilkinson[1,2], **Melissa L. Bondy**[2,3], **Xifeng Wu**[2], **Jian Wang**[2], **Qiong Dong**[2], **Anthony M. D'Amelio Jr.**[2], **Alexander V. Prokhorov**[2], **Xia Pu**[2], **Robert K. Yu**[2], **Carol J. Etzel**[2], **Sanjay Shete**[2], and **Margaret R. Spitz**[3]

[1]University of Texas School of Public Health, Austin Regional Campus, Austin TX78701

[2]University of Texas M.D. Anderson Center, Division of Cancer Prevention & Population Sciences, Houston, TX 77030

[3]Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX 77030

Abstract

Background—Established psychosocial risk factors increase the risk for experimentation among Mexican-origin youth. Now we comprehensively investigate the added contribution of select polymorphisms in candidate genetic pathways associated with sensation seeking, risk taking, and smoking phenotypes to predict experimentation.

Methods—Participants, (N=1,118 Mexican origin youth) recruited from a large population-based cohort study in Houston, Texas, provided prospective data on cigarette experimentation over three years. Psychosocial data were elicited twice—baseline and final follow-up. Participants were genotyped for 672 functional and tagging variants in the dopamine, serotonin and opioid pathways.

Results—After adjusting for gender and age, with a Bayesian False Discovery Probability set at 0.8 and prior probability of 0.05, six gene variants were significantly associated with risk of experimentation. After controlling for established risk factors, multivariable analyses revealed that participants with six or more risk alleles were 2.25 (95%CI: 1.62–3.13) times more likely to have experimented since baseline compared to participants with five or fewer. Among committed never smokers (N=872), three genes (*OPRM1, SNAP25, HTR1B*) were associated with experimentation as were all psychosocial factors. Among susceptible youth (N=246) older age at baseline, living with a smoker, and three different genes (*HTR2A, DRD2, SLC6A3*) predicted experimentation.

Conclusions—Our findings, which have implications for development of culturally-specific interventions, need to be validated in other ethnic groups.

Impact—These results suggest that variations in select genes interact with a cognitive predisposition toward smoking. In susceptible adolescents, the impact of the genetic variants appears to be larger compared to committed never smokers.

Introduction

Smoking remains the leading modifiable risk factor for lung cancer, increasing risk for the disease between 10- to 20-fold, depending on the duration and intensity (1). Moreover, compared to smoking initiation in late adolescence or early adulthood, early smoking initiation is associated with increased DNA damage in the lung (2) as well as higher levels

Corresponding Author: Anna Wilkinson, PhD, 1616 Guadalupe, Suite 6.300, Austin, Texas 78701, Anna.V.Wilkinson@uth.tmc.edu.

of nicotine dependence and more years smoked (3), all factors that increase the risk of developing lung cancer (2,4). The social, economic, and individual benefits to be gained by preventing youth from experimenting with cigarettes and becoming adult smokers are therefore profound.

Despite the large body of literature available on the prevalence of smoking behavior among US adolescents, research examining the transition from never smoking to experimentation (defined as having tried cigarettes, but not smoking on a monthly basis) with cigarettes is limited, especially among Hispanic adolescents. We (5), and others (6,7), have reported that cognitive susceptibility to smoking, a construct that combines peer social influence with behavioral intentions, is possibly the strongest single predictor of cigarette experimentation. We found that 45% of youth who self-reported as cognitively susceptible to smoking subsequently experimented with cigarettes, compared to 15% of their peers who self-reported as being committed never smokers (5). Understanding factors associated with this transition is crucial to smoking prevention efforts because up to 64% of experimenters transition to daily smoking within one year of starting (8), most make the transition to regular smoking by age 18 (9), and almost 90% of adults who currently smoke initially experimented with smoking when they were less than 18 years of age (10). Figure 1 presents transitions on the smoking continuum from committed never smoker, to susceptible, to experimenting, and finally regular smoking.

Hispanics are the largest and most rapidly increasing ethnic group in the United States, and those of Mexican origin comprise the majority of this subgroup (11). Nationally, Mexican origin youth report the highest rates of cognitive susceptibility to smoking – 29% compared to 21% in non-Hispanic whites and 23% in non-Hispanic blacks (12) and in Texas Hispanic adolescents exhibit the highest rates of experimentation with cigarettes among all ethnic groups – 55% compared to 48% in non-Hispanic whites and 46% in non-Hispanic blacks report ever experimenting with cigarettes (13), underscoring their increased risk for adult smoking.

In order to enhance prevention efforts in this growing population, we evaluated the trajectory from never smoking to experimenting with cigarettes in a longitudinal cohort of Mexican origin adolescents between 11 and 13 years of age at enrollment who were followed for five years. Among this sample of over a thousand youth, we have shown (5) that being a boy and older at enrollment, holding positive beliefs about the social benefits of smoking, living with a smoker, and having had at least one school detention all significantly predicted becoming an experimenter over the course of the four-year study. We also reported that baseline cognitive susceptibility to smoking status modified the relationship between experimentation at follow-up and the other established risk factors examined (5), suggesting that risk factors associated with experimentation vary by susceptibility status.

Contemporaneously, family, twin, candidate and genome wide association studies provide compelling evidence of a role for genetic variants governing smoking initiation, nicotine dependence and cessation (14,15) with estimated heritability rates ranging from 40–60% for initiation (16,17) and around 50% for persistence (18). We now expand our analysis to assess the role of 58 genes and 672 SNPs covering genetic variants in candidate pathways that influence sensation seeking behavior, risk taking behavior, and smoking phenotypes, in the context of established demographic and psychosocial risk factors, among these same youth during the transition from never-smoking to experimentation with cigarettes. We include SNPs associated with sensation seeking and risk taking behavior because both behaviors are associated with smoking initiation (19–21). Because our goal is to examine potential gene-environment interactions associated with the transition from never smoking

to experimenting with cigarettes, in the current study we focus on youth who had not experimented with cigarettes at baseline when they enrolled in the cohort.

Participants and Methods

Participant recruitment

Between May 2005 and December 2006, youth were recruited from a population-based cohort of Mexican-American households in the Houston metropolitan area. A detailed description of the cohort recruitment methodology has been published (22). A total of 3,000 households with potential age-eligible adolescents (11 to 13 years) were identified from the cohort database. Of the first 1,425 potential participants' parents or legal guardians contacted to assess interest in the study, just over 90% agreed to enroll their child (N=1,328). The institutional review board at M. D. Anderson Cancer Center approved all aspects of this study.

Data collection

Data on smoking phenotype were collected via personal interview on five sequential encounters. Baseline and final interviews were completed in the home -- the second home survey was completed 30 months (SD=4.8 months) after baseline. The second, third and fourth interviews, were completed roughly 6, 12, and 18 months respectively following baseline, over the telephone. At baseline, after consenting into the study, each participant completed a 5-minute personal interview during which basic demographic (gender, age, nativity status (US or Mexico)) acculturation data (23), and parental educational attainment (available for 93.5% of the study participants) were collected. To assure confidentiality from parents overhearing the child's responses, the remainder of the survey was completed on a personal digital assistant (PDA). All participants provided buccal samples at baseline. A detailed description of baseline data collection procedures has been published (24).

Measures

Our primary outcome variable was new experimentation with cigarettes, assessed using two questions derived from the Youth Risk Behavior Surveillance Survey (25), "Have you ever smoked a whole cigarette?" and "Have you ever tried a cigarette, even a puff?" Participants who answered "yes" to either question were defined as experimenters. All others were considered never experimenters. Participants who responded "no" at baseline, but "yes" to either question at any follow-up were designated as 'new experimenters.'

We further examined the influence of several established psychosocial risk factors: risk taking tendencies (21), outcome expectations related to smoking (26), household social influence (27–29), and cognitive susceptibility to smoking (5,7). The measures used to assess these constructs are detailed in Table 1.

DNA collection

Saliva samples were obtained in Oragene vials (DNA Genotek, Ottawa, Ontario, Canada). DNA extraction was performed using a "Purifier" solution with alcohol precipitation per the manufacturer's protocol. The median yield of DNA from 2 mL of saliva captured in 2 mL of Oragene•DNA was 110 μg.

SNP selection

Candidate genes were identified from published reviews (e.g. 30) and pub-med searches using the following key words: sensation seeking, risk taking, gambling, smoking onset and initiation. This list was cross-referenced with the Gene Ontology Database (31) and Kegg

Pathway to confirm pathway information. Tagging SNPs were selected from the International HapMap Project (Release 21 with NCBI build 36; 32). The following selection criteria were used: located in the respective gene or within 10 kb upstream or downstream of the gene ends to cover the regulatory regions; minor allele frequency (MAF) >5% in various ethnic groups; and not already represented by a current tag SNP at an LD of r^2>0.80. We also included SNPs in coding (synonymous SNPs, nonsynonymous SNPs) and regulatory regions (promoter, splicing site, 5-UTR, and 3-UTR). In addition, functional SNPs and SNPs previously reported to be associated with smoking phenotypes were included. The gene, position, allelic change and chromosome are summarized in Supplemental Table 1.

Genotyping

A total of 1274 samples were sent for genotyping. We designed an Illumina GoldenGate assay for candidate SNPs (Illumina, San Diego, California). Ninety-three percent of the SNPs had Illumina SNP scores of >0.6. DNA samples (250 ng) were genotyped following the standard three-day Illumina protocol. Data from the array were autocalled by the BeadArray Reader (Illumina Inc). Cluster definitions for each SNP were determined using Illumina BeadStudio Genotyping Module v 2.3.41. Genotype calls were made when a genotype yielded a quality score (Gencall value) of 95% or higher. Among these markers, 1.2% of calls were missing (8 out of 672). Seventy blind duplicate pairs were included, and the concordance of SNP genotype calls was greater than 99%.

Statistical analyses

Chi-square tests were used to examine associations between experimenter status and both categorical demographic and smoking-related covariates. Student's t-tests and one-way analysis of variance were used to examine mean differences on the continuous covariates. Linkage disequilibrium (LD) between SNPs was assessed by calculating pairwise Lewontin's D′ and r^2 using Haploview version 3.32.

Two multivariable models were developed (one with and one without genotype data). Psychosocial risk factors with a significant bivariate association ($p<0.05$) with new experimenting were entered into unconditional logistic regression analyses. We used Bayesian False Discovery Probability tests (BFDP; 33) to evaluate the chance of false positive associations for the variants studied. We set four levels of prior probability (0.01, 0.03, 0.05, and 0.07), prior odds ratio (OR) at 1.5, and the selected level of noteworthiness for BFDP at 0.8, the recommended threshold by Wakefield (33).

Because a priori we do not know the mode of inheritance, we tested each significant SNP using dominant, recessive, and additive models and selected the most parsimonious. SNPs retained in the multivariable model were summed to create a genetic risk score. SNPs that exhibited a protective effect were reverse coded prior to creating the genetic risk score. Thus, higher scores on the genetic risk score reflected increased risk.

Next principle components analysis was performed to test for the possible underlying ethnic stratification, with the use of EIGENSTRAT software (34). We first applied the principal components analysis to the genotype data to infer continuous axes of genetic variation, which are defined as eigenvectors. We then employed the top axes of variation as the covariates in the unconditional logistic regressions to develop the multivariable models.

Finally, having determined that cognitive susceptibility modifies the influence of the psychosocial variables on experimentation (5) and because including the genotype data did not significantly attenuate the odds ratios derived from the first model, we applied a standard methodology (35,36) to determine if cognitive susceptibility to smoking moderated (modified) the influence of the genotype data on experimentation. The interaction term

(cognitive susceptibility by genetic risk score) and the main effects were simultaneously entered into unconditional logistic regression models. The interaction reflects the interaction between putative risk alleles and being cognitively susceptible to smoking.

Results

DNA from 1,274 youth enrolled was available for analysis. The 120 youth who reported experimenting at baseline were excluded as were an additional 36 for whom complete follow-up information was missing. The final sample size was 1,118; 584 (52.2%) were girls.

Table 2 summarizes demographic characteristics and psychosocial risk factors. Of the 211 (18.9%) participants who began experimenting over the course of the study, 62.6% were boys compared with 44.3% for never experimenters ($p<0.001$). Experimenters were significantly more likely to be 13 at baseline (42.7% vs. 21.3%; $p<0.001$) and live with at least one smoker (55.4% vs. 35.3%; $p<0.001$). A higher proportion of experimenters held positive outcome expectations about smoking (56.9% vs. 34.6%; $p<0.001$), reported risk taking tendencies (70.1% vs. 50.5%; $p<0.001$), and being cognitively susceptible to smoking (43.6% vs. 17.0%) than never experimenters.

Genotyping was completed on a total of 672 SNPs; eight SNPs had missing genotype data for all participants, 12 SNPs failed the Hardy Weinberg Equilibrium Test ($p<0.00001$) for the entire data set, and 86 SNPs failed the frequency test (MAF<0.05). Thus 574 SNPs were included in the analysis. There were 38 SNPs with $p<0.05$ based on the best model fit (additive, dominant, or recessive model). After controlling for false discovery, we identified 12 SNPs with a statistically significant BFDP at 0.8 and prior probability of 0.05. Finally using unconditional logistic regression analysis with backward selection and adjusting for age and sex, 6 of the 12 SNPs were selected at $p\leq0.05$. Table 3 presents the distribution of the six SNPs retained for the multivariable analyses – three in the dopamine pathway (rs12422191 on *DRD2*, rs10052016 on *SLC6A3*, and rs8119844 on *SNAP25*), two in the serotonin pathway (rs6297 on *HTR1B* and rs9567732 on *HTR2A*), and an opioid receptor variant (rs9322451 on *OPMR1*).

To perform the principle components analysis, we used N=1,118 participants and 536 SNPs, which were shown to be un-associated with the experimentation outcome at a significance level 0.05 based on the best model fit (additive, dominant, or recessive model). We did not observe significant ethnic stratification in our data from the principle components analysis. Because only the top two eigenvalues (derived from the top two principle components) were significantly larger than the subsequent eigenvalues, we used these two largest principle components in our analyses (Tables 4a and 4b; 37,38). We also considered controlling for the top three and top ten largest principal components, but found no significant differences in the resulting multivariable models.

Including the genes in the model (Table 4a) did not significantly attenuate the impact of the psychosocial factors as seen by overlapping confidence intervals. Being cognitively susceptible to smoking was the strongest predictor of new experimentation (OR=2.55; 95% CI: 1.74–3.73), followed by being 13 at baseline (OR=2.27; 95% CI: 1.59–3.23), male (OR=1.96; 95% CI: 1.40–2.75), holding positive outcome expectations about smoking (OR=1.65; 95% CI: 1.07–2.53), living with somebody who smokes (OR=1.53; 95% CI: 1.23–1.90) and exhibiting risk taking tendencies (OR=1.30; 95% CI: 1.07–1.59). All six SNPs were significantly associated with new experimentation. Four SNPs, within genes rs9322451 on *OPMR1* (OR=0.53; 95% CI: 0.35–0.81), rs10052016 on *SLC6A3* (OR=0.64; 95% CI: 0.45–0.90), rs9567732 on *HTR2A* (OR=0.70; 95% CI: 0.50–0.98) and rs8119844

on *SNAP25* (OR=0.26; 95% CI: 0.11–0.61) were protective, while two others, specifically rs6297 on *HTR1B* (OR=1.89; 95% CI: 1.17–3.03) and rs12422191 on *DRD2* (OR=2.10; 95% CI: 1.31–3.36) were associated with increased risk. Participants who carried six risk alleles were just over two times (OR=2.25; 95% CI: 1.62–3.13) more likely to have experimented since baseline, compared to participants with five or fewer risk alleles (data not shown).

The interaction (cognitive susceptibility by genetic risk score) was significant (OR=1.59; 95% CI: 1.06–2.39; data not shown), therefore, we stratified by cognitive susceptibility status (Table 4b). We found that among committed never smokers, all psychosocial variables maintained statistical significance as did three SNPs: rs9322451 on *OPRM1* (OR=0.55; 95% CI: 0.33–0.94), rs6297 on *HTR1B* (OR=2.10; 95% CI: 1.20–3.66) and rs8119844 on the *SNAP25* gene (OR=0.21; 95% CI: 0.08–0.53). However, among susceptible youth, only two of the variables maintained significance (being 13 years at baseline and living with a smoker), as did three different SNPs, specifically, rs10052016 on *SLC6A3* (OR=0.37; 95% CI: 0.20–0.68), rs9567732 on *HTR2A* (OR=0.46; 95% CI: 0.25–0.86), and rs12422191 on *DRD2* (OR=4.88; 95% CI: 2.89–12.56).

In each model adding the genetic information to the psychosocial factors increased the area under the Receiver Operating Characteristic (ROC) curve (Table 5), this increase was greatest in the model based on susceptible youth only. Among susceptible youth, adding the genetic information resulted in a 7% AUC increase from 69% (95% CI: 62–76) to 76% (95% CI: 70–82), compared to a 4% AUC increase from 70% (95% CI: 65–75) to 74% (95% CI: 69–79) among the committed never smokers (or non-susceptible youth).

Discussion

In this longitudinal study, we evaluated the added predictive value of select variants of candidate smoking-related phenotype genes in the dopamine, serotonin and opioid pathways on smoking experimentation as well as the impact of gene-environment interaction. Our results confirm the relationship between experimenting with cigarettes and established psychosocial and demographic risk factors and identify six SNPs significantly associated with new experimentation: three in the dopamine pathway, two in the serotonin pathway and an opioid receptor. Adding these SNPs to the multivariable models significantly improved the risk prediction of each model examined. Participants who carried six risk alleles were two times more likely to have experimented since baseline, compared to participants with five or fewer risk alleles. Our overall experimentation rate of 26.3%, and 44.3% among those who were 13 at baseline, appears comparable to rates reported elsewhere. In Brazil, 30% of 7th to 10th grade (39) and up to 50% of 15 to 16 year-old European students (40) report experimenting

Overall cognitive susceptibility to smoking, a psychosocial risk factor that assesses both peer influence and behavioral intentions (7) and an early phase in the transition from never to ever smoking (5) was the strongest psychosocial risk factor (over 2-fold) for experimentation. Risk factors associated with being susceptible to smoking include having friends who smoke, living with a smoker, having lower subjective social status and more detentions at school, and reporting more temptations to try smoking (41). We, and others, have shown that smoking initiation is strongly influenced by gender and age (5,42,43). Higher perceived outcome expectations, which assess the perceived social benefits from smoking, are associated with both intentions to smoke (44) and experimenting with cigarettes (5,45). Our data confirmed a roughly 70% increased risk of experimenting associated with positive outcome expectations. Among committed never smokers only, the risk increased to almost 3-fold and holding positive outcome expectations exerted the

strongest independent influence on experimenting among all psychosocial risk factors examined. Having a parent who smokes is a strong, consistent predictor of smoking initiation among youth (27–29). Consistent with previous work, risk taking tendencies, which tend to peak in adolescences (46), predicted experimentation (20,47,48).

Next we focus on the results from the stratified analyses. Among committed never smokers three of the SNPs (*OPRM1, SNAP25, HTR1B*) were associated with experimentation as were all the psychosocial factors. However, among susceptible youth, it appears that the psychosocial factors are less relevant because only increasing age and living with a smoker had an impact. In addition, three different SNPs (*HTR2A, DRD2, SLC6A3*) were associated with experimentation in this subgroup. Adding the genetic data improved the predictiveness of both models as assessed by the area under the curve; this improvement was more marked among susceptible participants. It must be noted that these genetic variants are not predicting a response to nicotine, rather sensation seeking, risk taking or curiosity, as this analysis only included participants who had not tried cigarettes at baseline. In summary, psychosocial risk factors appear to be more important predictors of experimenting among the committed never smokers (non-susceptible youth) relative to the susceptible youth, based on previous work (5) and the current analysis. The genetic risk factors appear to be more important predictors of experimenting among the susceptible youth than the committed never smokers, as fewer psychosocial risk factors maintained significance among the susceptible youth compared to committed never smokers.

The dopaminergic system is important in mediating the pleasurable feelings of reward and novelty seeking behavior. Individuals with a high level of such behaviors are likely to be more susceptible to cues for potential reward, such as initiating smoking. We found that a SNP on *DRD2* (rs12422191) was significantly associated with new experimentation; in the analysis stratified on susceptibility status, *DRD2* maintained significance among participants identified as susceptible to smoking only, among whom this variant exhibited the strongest association with smoking behavior (OR=4.88) among all genes and psychosocial factors examined.

There are conflicting reports about the association between *DRD2* and smoking behavior among both adolescents and adults (49–52). Among adults, we found rs1800497 on *DRD2* (which is in perfect LD with rs12422191 for both CEU and Mexican populations) was associated with continuation of smoking. Carriers of the rare allele are reported to exhibit an earlier age at onset of smoking (51) and in an adolescent Caucasian population, to be associated with progression to smoking (53). Neuroimaging findings support a functional role of the gene in regulation of *DRD2* availability in the frontal cortex (54), and Noble (55) has shown that carriers of at least one variant allele have 40% fewer receptors relative to wildtype carriers.

The dopamine transporter gene (*SLC6A3*) regulates dopamine reuptake into presynaptic terminals and has also been studied extensively in relation to smoking behavior and cessation (56). We found the rare allele of *SLC6A3* (rs10052016) to be protective against experimentation in susceptible participants. The 9 repeat allele of *SLC6A3* VNTR sequence in the 3’ UTR has previously shown to have a protective in several diverse populations, including young Israeli women (57) and adolescents (58).

The opioid receptors and their endogenous ligands have long been implicated in addiction, sensation seeking behaviors, and smoking initiation (59). The *OPMR1* variant had a protective effect among the full sample and among committed never smokers, but was not significantly associated with new experimentation among susceptible youth.

Gene variants in serotonin receptors are logical candidates for studying inter-individual variation in smoking initiation, since the neurotransmitter plays a role in modulating social behavior. The 5-hydroxytryptamine (serotonin) receptor *HTR1B* variant, rs6297, was associated with an increased risk of new experimentation among the full sample (OR=1.89) and just over a two-fold increased risk of new experimentation among the committed never smokers. This synonomous exonic SNP has been associated with aggressive behavior in children (60), and impulsivity, although not consistently (61).

The SNAP complex mediates presynaptic vesicle trafficking and participates in the release of dopamine and other neurotransmitters (62). The *SNAP25* (rs8119844) variant exhibited the strongest association with new experimentation of any of the genes and psychosocial factors we examined in the overall analysis, and among committed never smokers. Committed never smokers who carry the minor AA allele are almost five times more likely to have tried cigarettes than their peers. To the best of our knowledge, the relationship between *SNAP25* and experimenting with cigarettes has not been reported in the literature before. However, *SNAP25* is associated with negative affect (62) and with ADHD (63), both of which are associated with an increased risk for smoking among adolescents (64,65).

The current study has both strengths and limitations. The prospective design allowed us to examine experimentation at follow-up among participants who had not experimented at baseline and to test for moderation effects. Further, participants were from a population-based cohort and included roughly equal numbers of girls and boys. All psychosocial constructs were assessed using validated measures, and data were collected using PDAs to ensure participant privacy and quality of the data. The participants represent a large ethnically homogenous and predominantly low-income sample of Mexican origin youth, an understudied population. A final strength is the high retention rate: 87% of the youth provided data on all five contacts.

Conversely, the main limitation of this study is the lack of an independent replication sample; thus we must consider our findings preliminary. However given the large number of SNPs tested, we did adjust the significance level for each SNP included in this analysis using a BFDP approach (30). Although the percent of SNPs failing the H-W test is higher than expected, we did not observe a systematic pattern with regards the SNPs that failed suggesting it did not impact our results. A third limitation is that participants were all of Mexican origin, and results may not generalize to other ethnicities. In addition, we did not have biochemical validation of the participants' smoking status (e.g., salivary cotinine). However, we informed participants during the consent process that they might be selected to provide a saliva sample to check their smoking status; this "bogus pipeline" procedure has been shown to increase the validity of self-reported smoking status (66).

Conclusion

This is one of the first studies to examine the role of both genetic and non-genetic factors associated with the transition from never smoking to cigarette experimentation among Mexican origin youth. The results confirm and extend previous findings (e.g. the strong association between *SNAP25* and experimenting) and suggest that the impact of both psychosocial and genetic factors differs depending upon the susceptibility status of the adolescents. Our results need to be confirmed with an independent sample of Mexican origin youth (in particular with regards to *SNAP25* as in general with recessive genes the number of risk SNPs is smaller compared to dominant) and among youth of other ethnic backgrounds, as they have implications for development of culturally-specific interventions. In conclusion, with regards the genes we identified, which are related to the very beginning of the smoking trajectory, when youth are contemplating whether to try cigarettes (i.e. risk

of experimentation), there appear to be differences in genotype between youth who think they will try cigarettes compared to their peers who think they will not try cigarettes in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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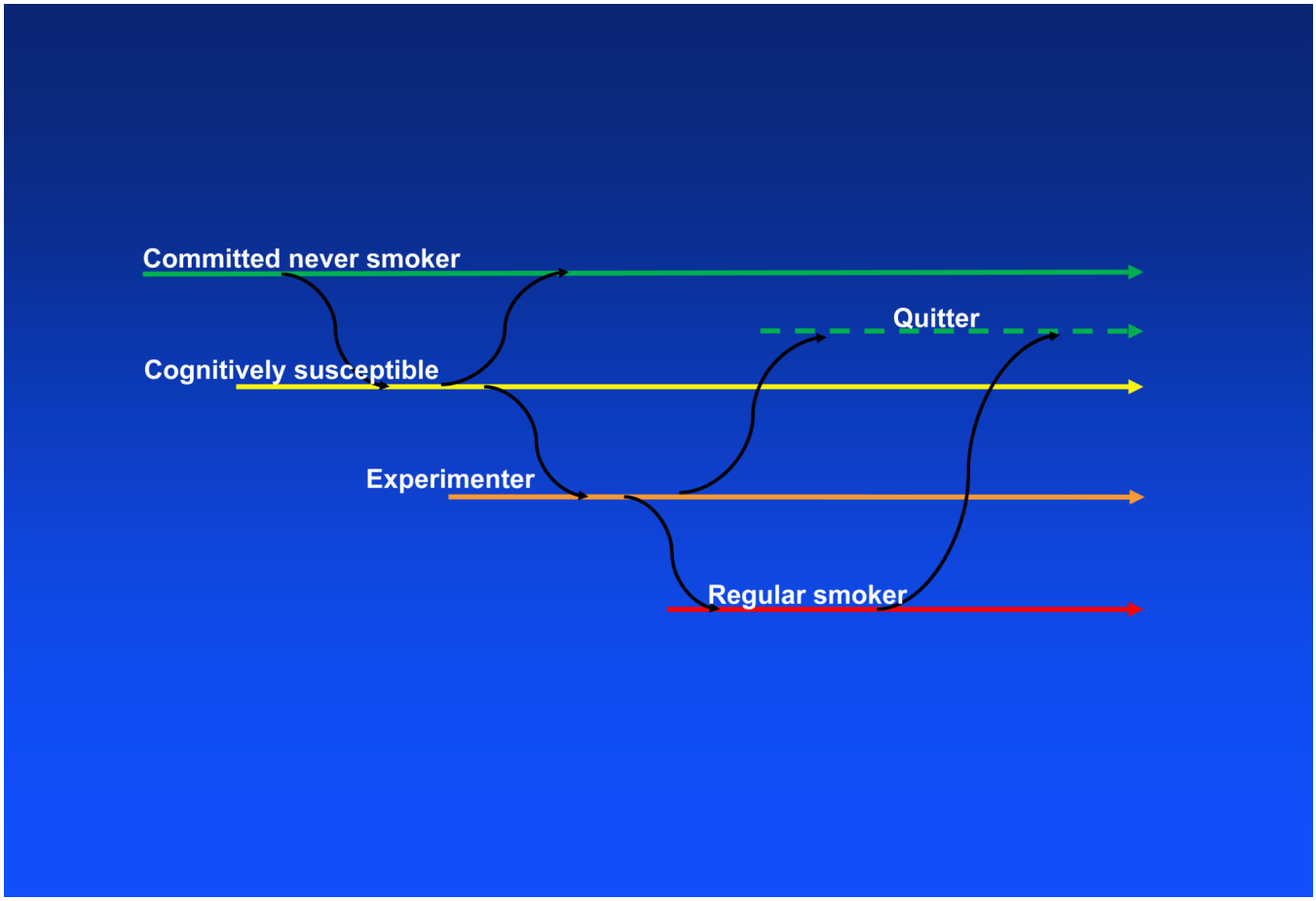

Figure 1.
Movement between cognitive susceptibility, experimentation and regular smoking over time

Table 1

Description of the psychosocial measures used to assess each construct

Construct	Description
Linguistic acculturation	Assessed at baseline using 4 items from the Language Use subscale of the Brief Acculturation Scale for Hispanics (23), which ascertains language used when reading, speaking at home, with friends, and thinking. This scale had good internal reliability (alpha=0.76).
Risk taking	Assessed using two items “I look for dangerous things to do, just for excitement” and “If I got a chance to skydive from an airplane, I’d do it.” Responses were made on a four-point scale ranging from “just like me” to “not at all like me” and were averaged. For descriptive purposes the variable was categorized into “high” and “low” based on the median split, in the multivariable analysis it was entered as continuous. Higher scores indicate greater risk taking tendencies.
Outcome expectations	Assessed at baseline using a 7-item scale developed by Dalton et al (26). Examples include “I think smoking would help me to feel more comfortable at parties” and “I think smoking would make me look more mature.” Responses are made on a 4-point scale ranging from “strongly disagree” to “strongly agree.” We have found the scale to have good internal consistency (Cronbach’s alpha = 0.86). For descriptive purposes the variable was categorized into “none” and “some” however, in the multivariable analysis it was entered as continuous. Higher scores indicate more positive perceived consequences ascribed to smoking behavior.
Household social influence	For each potential household member (i.e. father, mother, sister(s), brother(s), and other(s)) the participant was asked “Does your father smoke?” and “Do you live with your father?” To ensure the variable reflected social influence from all household members with whom the participant currently lived, we summed the number of smoking household members residing with participant. In the multivariable analyses this variable was coded as “none” and “at least one,” with “none” serving as the reference category.
Cognitive susceptibility	Combines behavioral intentions and peer influence and was assessed among never-smokers only (7). To be coded as “non-susceptible” participants responded “no” to “Do you think you will try a cigarette soon?”; and “definitely not” to “If one of your best friends were to offer you a cigarette would you smoke it?” & “Do you think you will be smoking cigarettes 1 year from now?” All other participants were coded as susceptible.

Table 2

Distribution of demographic characteristics and smoking-related covariates by new experimenter status (N=1,118).

		Experimenter Status		
		New Experimenter	Never Experimenter	
	N (%)	N (%)	N (%)	p-value
Overall	1,118 (100.0)	211 (18.9)	907 (81.1)	
Demographic Characteristics				
Gender				
Females	584 (52.2)	79 (37.4)	505 (55.7)	
Males	534 (47.8)	132 (62.6)	402 (44.3)	< 0.001
Age (years)				
11 or 12	835 (74.7)	121 (57.3)	714 (78.7)	
13	283 (25.3)	90 (42.7)	193 (21.3)	< 0.001
Mean (SD)	11.89 (0.84)	12.18 (0.87)	11.75 (0.80)	< 0.001
Country of birth				
Mexico	297 (26.6)	48 (22.7)	249 (27.5)	
US	821 (73.4)	163 (77.3)	658 (72.5)	0.16
Linguistic acculturation				
Low	256 (22.9)	41 (19.4)	215 (23.8)	
High	861 (77.1)	170 (80.6)	691 (76.2)	0.18
Parental education (N=1,051)				
< HS	619 (65.6)	64 (32.3)	301 (35.3)	
≥ HS grad	324 (34.4)	134 (67.7)	552 (64.7)	0.43
Smoking-related Covariates				
No. of household members who smoke				
None	681 (60.9)	94 (44.6)	587 (64.7)	
One	341 (30.5)	84 (39.8)	257 (28.4)	
≥ Two	96 (8.6)	33 (15.6)	63 (6.9)	< 0.001
Mean (SD)	0.55 (0.76)	0.75 (0.84)	0.43 (0.66)	< 0.001
Risk taking				
Averse	512 (45.8)	63 (29 9)	449 (49.5)	
Some	606 (54.2)	148 (70.1)	458 (50.5)	< 0.001
Mean (SD)	1.68 (0.81)	1.95 (0.90)	1.58 (0.76)	< 0.001
Outcome expectations				
None	684 (61.2)	91 (43.1)	593 (65.4)	
Some	434 (38.8)	120 (56.9)	314 (34.6)	< 0.001
Mean (SD)	1.26 (0.40)	1.35 (0.42)	1.19 (0.35)	< 0.001
Susceptible at baseline				
No	872 (78.0)	119 (56.4)	753 (83.0)	
Yes	246 (22.0)	92 (43.6)	154 (17.0)	< 0.001

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Table 3

Distribution of genes by new experimenter status (N=1,118)

Genes	M*	Experimenter Status				HapMap minor allele	MATCh minor allele
			New Experimenter	Never Experimenter			
		N (%)	N (%)	N (%)	p-value	%	%
		1,118 (100.0)	211 (18.9)	907 (81.1)			
OPRM1 (rs9322451)	D						
0		822 (73.5)	174 (21.2)	648 (78.8)			
1		296 (26.5)	37 (12.5)	259 (87.5)	0.001	16.7	14.4
HTR1B (rs6297)	D						
0		990 (88.6)	117 (17.9)	813 (82.1)			
1		128 (11.4)	34 (26.6)	94 (73.4)	0.018	8.3	5.9
SNAP25 (rs8119844)	R						
0		1,089 (97.4)	200 (18.4)	889 (81.6)			
1		29 (2.6)	11 (37.9)	18 (62.1)	0.008	15.0	16.1
SLC6A3 (rs10052016)	D						
0		620 (55.5)	133 (21.5)	487 (78.5)			
1		498 (44.5)	78 (15.7)	420 (84.3)	0.014	77.0	74.8
HTR2A (rs9567732)	D						
0		530 (47.7)	117 (22.1)	413 (77.9)			
1		588 (52.6)	94 (16.0)	494 (84.0)	0.009	--	--
DRD2 (rs12422191)	D						
0		980 (87.7)	175 (17.9)	805 (82.1)			
1		138 (12.3)	36 (26.1)	102 (73.9)	0.021	5.0	6.6

NB: M = Model; D = Dominant, R = Recessive

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Table 4

a: Logistic Regression for New Experimentation (N=1118)

	Psychosocial factors only			Psychosocial and genetic factors		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Social and psychological factors						
Cognitively susceptible	2.34	1.62 – 3.37	< 0.001	2.55	1.74 – 3.73	< 0.001
Age 13 at baseline	2.13	1.51 – 2.99	< 0.001	2.27	1.59 – 3.23	< 0.001
Male	1.87	1.35 – 2.59	< 0.001	1.96	1.40 – 2.75	< 0.001
Outcome expectations	1.69	1.11 – 2.57	0.014	1.65	1.07 – 2.53	0.023
Household member smokes	1.51	1.22 – 1.86	< 0.001	1.53	1.23 – 1.90	< 0.001
Risk taking tendencies	1.35	1.12 – 1.64	0.002	1.30	1.07 – 1.59	0.009
Gene (SNP)						
SNAP25 (rs8119844)	–	–	–	0.26	0.11 – 0.61	0.002
OPRM1 (rs9322451)	–	–	–	0.53	0.35 – 0.81	0.003
HTR1B (rs6297)	–	–	–	1.89	1.17 – 3.03	0.009
SLC6A3 (rs10052016)	–	–	–	0.64	0.45 – 0.90	0.009
HTR2A (rs9567732)	–	–	–	0.70	0.50 – 0.98	0.038
DRD2 (rs12422191)	–	–	–	2.10	1.31 – 3.36	0.002
AIC Criteria		958.41			930.10	

b: Logistic Regression for New Experimentation Stratified by Cognitive Susceptibility

	Committed Never Smoker (N = 872)			Susceptible (N = 246)		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Social and psychological factors						
Age 13 at baseline	2.04	1.31 – 3.20	0.002	3.00	1.61 – 5.62	0.001
Male	2.08	1.37 – 3.17	0.001	1.64	0.89 – 3.02	0.116
Outcome expectations	2.87	1.63 – 5.06	< 0.001	0.93	0.48 – 1.80	0.825
Household member smokes	1.52	1.15 – 2.01	0.003	1.63	1.12 – 2.38	0.011
Risk taking tendencies	1.46	1.14 – 1.88	0.003	1.17	0.83 – 1.64	0.379

b: Logistic Regression for New Experimentation Stratified by Cognitive Susceptibility

	Committed Never Smoker (N = 872)			Susceptible (N = 246)		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Gene (SNP)						
SNAP25 (rs8119844)	0.21	0.08 – 0.53	0.001	0.42	0.04 – 4.10	0.454
OPRM1 (rs9322451)	0.54	0.32 – 0.92	0.025	0.54	0.26 – 1.11	0.095
HTR1B (rs6297)	2.10	1.20 – 3.66	0.009	1.44	0.58 – 3.58	0.433
SLC6A3 (rs10052016)	0.85	0.56 – 1.28	0.429	0.37	0.20 – 0.68	0.002
HTR2A (rs9567732)	0.80	0.53 – 1.21	0.287	0.46	0.25 – 0.86	0.015
DRD2 (rs12422191)	1.49	0.81 – 2.74	0.199	4.88	1.89 – 12.56	0.001
AIC Criteria		640.95			291.66	

•New experimentation includes participants who reported that they had not experimented at baseline and reported that they had experimented on one or more of the four subsequent contacts.

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Table 5

Area Under the Curve (AUC) and 95% CI for each model's ROC Curve

	Psychosocial factors only		Psychosocial and genetic factors	
	AUC	**95% CI**	**AUC**	**95% CI**
All	0.74	0.70 – 0.78	0.77	0.73 – 0.81
Committed Never Smoker	0.70	0.65 – 0.75	0.74	0.69 – 0.79
Susceptible	0.69	0.62 – 0.76	0.76	0.70 – 0.82