

A Genetic Association for Cigarette Smoking Behavior

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Dopaminergic genes are likely candidates for heritable influences on cigarette smoking. In an accompanying article, Lerman et al. (1999) report associations between allele 9 of a dopamine transporter gene polymorphism (SLC6A3-9) and lack of smoking, late initiation of smoking, and length of quitting attempts. The present investigation extended their study by examining both smoking behavior and personality traits in a diverse population of nonsmokers, current smokers, and former smokers ($N = 1,107$). A significant association between SLC6A3-9 and smoking status was confirmed and was due to an effect on cessation rather than initiation. The SLC6A3-9 polymorphism was also associated with low scores for novelty seeking, which was the most significant personality correlate of smoking cessation. It is hypothesized that individuals carrying the SLC6A3-9 polymorphism have altered dopamine transmission, which reduces their need for novelty and reward by external stimuli, including cigarettes.

Key words: smoking, SLC6A3 gene, dopamine, personality

Although more than 80% of smokers would like to quit, far fewer succeed. Even the most carefully planned smoking cessation programs rarely have success rates higher than 10% to 20% after 1 year, representing relapse rates similar to those for heroin (Benfari, Ockene, & McIntyre, 1982).

The reinforcing properties of nicotine are in part due to activation of the mesolimbic dopamine reward system and release of dopamine in the nucleus accumbens, the brain's pleasure and reward center (Carr, Basham, York, & Rowell, 1992; Di Chiara & Imperato, 1988; Pontieri, Tanda, Orzi, & Di Chiara, 1996). This mechanism is shared by many

different addictive drugs; for example, brain scans of rats ingesting nicotine are essentially indistinguishable from those of rats ingesting cocaine (Pontieri et al., 1996). Cigarette smoke also contains substances that inhibit brain monoamine oxidase B, which degrades dopamine and other monoamine neurotransmitters (Fowler et al., 1996).

Behavioral genetics research has shown that individual differences in smoking behavior are substantially heritable. In one investigation, the concordance for smoking in 42 pairs of identical twins reared apart was 79% (Shields, 1962), and a meta-analysis of the data from five studies, each involving more than 1,000 twin pairs, showed an estimated heritability of 60% for the propensity to smoke (Heath & Madden, 1995). Twin studies have also shown that the genetic factors involved in the initiation and cessation of smoking are partially overlapping but mostly independent (Heath & Martin, 1993).

The link between dopamine release and the addictive properties of nicotine point to dopaminergic genes as logical candidates for genetic effects on smoking behavior. In support of this idea, Lerman et al. (1999) demonstrated an association between smoking behavior and allele 9 of a 3' untranslated region polymorphism in the dopamine transporter gene (SLC6A3-9) in their case-control study of nonsmokers and current smokers. They found that individuals with an SLC6A3-9 genotype were less likely to be smokers than individuals without allele 9 and that smokers with SLC6A3-9 genotypes had started to smoke later and had been able to quit for longer periods of time than other smokers.

The current study was designed to extend the findings of

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Lerman et al. (1999) in two ways. First, we analyzed former smokers as well as current smokers and nonsmokers. This was done to determine whether the association between the SLC6A3 gene and smoking status is due to an effect on smoking initiation, which can be analyzed by comparing current and former smokers with nonsmokers, or to an effect on smoking cessation, which can be analyzed by comparing former and current smokers. This distinction could not be made in the design used by Lerman et al. (1999), because former smokers were not included.

Second, we administered personality inventories to a portion of the participants. This was done to test the hypothesis that the SLC6A3 gene is associated with smoking behavior through an effect on personality traits. Previous studies have shown that certain personality traits contribute to both smoking initiation and cessation and account for some of the genetic influences on smoking behavior (Barefoot, Smith, Dahlstrom, & Williams, 1989; Lipkus, Barefoot, Williams, & Siegler, 1994; Patton, Barnes, & Murray, 1993). Personality traits were measured with the Temperament and Character Inventory (TCI), an instrument based on a biosocial model of personality postulating four genetically influenced dimensions of temperament: novelty seeking, harm avoidance, reward dependence, and persistence (Cloninger, Przybeck, Svrakic, & Wetzel, 1994). We hypothesized that the SLC6A3 gene would be associated with smoking behavior through novelty seeking because this personality trait is thought to be modulated by dopamine (Cloninger, 1994; Cloninger, Svrakic, & Przybeck, 1993) and has been linked to cigarette smoking behavior (Heath, Madden, Slutske, & Martin, 1995; Menza, Golbe, Cody, & Forman, 1993; Pomerleau, Pomerleau, Flessland, & Basson, 1992).

Method

Participants

The study population consisted of 1,107 individuals ascertained through National Institutes of Health (NIH) protocols on cancer-risk-related behaviors ($n = 124$), personality genetics ($n = 431$; Benjamin et al., 1996; Lesch et al., 1996), and sexual behavior ($n = 552$; Hamer, Hu, Magnuson, Hu, & Pattatucci, 1993; Hu et al., 1995; Pattatucci & Hamer, 1995). These protocols were approved by the appropriate NIH institutional review boards, and informed consent was obtained from all participants. In the combined samples, the gender distribution was 55% male and 45% female, the average age was 33.7 years ($SD = 13.5$, range = 18–84), the average educational level was 16.2 years ($SD = 2.7$, range = 6–20), the average Kinsey score was 2.17 ($SD = 2.6$, range = 0–6), and the ethnic composition was 83.9% White non-Hispanic, 4.2% Asian-Pacific Islander, 4.6% Hispanic-Latino, 4.4% African American-Black, 0.4% Native American-Alaskan, and 2.5% other. Each of the protocols was designed to analyze same-sex sibling pairs and other family members, and the family composition of the sample was 964 siblings from 439 families, 75 parents, and 65 unrelated individuals. Families for the cancer-risk-related behaviors protocol were selected on the basis of having at least one sibling who was a heavy smoker, whereas those for the other protocols were recruited without regard to smoking status.

Measures

All participants completed a structured interview or questionnaire that stratified them into three categories with regard to smoking status: nonsmokers ($n = 593$; 53.6%), current smokers ($n = 283$; 25.6%), and former smokers ($n = 231$; 20.9%). A detailed smoking inventory that included age at smoking initiation, smoking rate, and history of cessation attempts was administered starting in 1995 and was completed by 604 of the participants. Among the participants who completed the more detailed questionnaire, the nonsmokers had all smoked fewer than 100 cigarettes in their lifetime (and thus could be considered as never smokers); the current smokers had started smoking at 14.9 ($SD = 3.6$) years of age, had been smoking for 16.5 ($SD = 12.0$) years, and currently smoked 19.9 ($SD = 12.2$) cigarettes per day; the former smokers had started smoking at 15.5 ($SD = 11.5$) years of age, had smoked for 12.2 ($SD = 11.5$) years, had previously smoked 19.0 ($SD = 14.9$) cigarettes per day, and had been abstinent for an average of 11.3 ($SD = 9.9$) years.

TCIs were administered starting in 1995 and were completed by 515 of the participants. The TCI is a 240-item true-false self-report questionnaire designed to measure four temperamental factors and three character traits (Cloninger et al., 1994). Only the data for the temperamental factors, which have been demonstrated to be heritable (Heath, Cloninger, & Martin, 1994; Stallings, Hewitt, Cloninger, Heath, & Eaves, 1996), are considered here. Participants also completed the Revised NEO Personality Inventory, but no significant associations with SLC6A3 genotype were found.

Genotyping and Statistical Analyses

DNA was extracted from peripheral blood, and SLC6A3 3' variable number of tandem repeat (VNTR) genotypes were determined by polymerase chain reaction amplification and agarose gel electrophoresis (Vandenbergh et al., 1992). Allele frequencies were similar to those found in other reports: allele 9, 26.7%; allele 10, 72.5%; and other, 0.8% (Comings et al., 1996b; Cook et al., 1995; Doucette-Stamm, Blakey, Tian, Mockus, & Mao, 1995; Gelernter, Kanzler, Satel, & Rao, 1994). Based on the results of Lerman et al. (1999), genotypes were dichotomized according to whether they contained allele 9 (9/9 and 9/*; $n = 497$; 44.9%) or lacked allele 9 (*/*; $n = 610$; 55.1%). The DRD2-A1/A2 polymorphism was genotyped in 738 participants and classified according to the presence or absence of allele A1 (Lerman et al., 1999).

Statistical analyses were conducted with SPSS and SAS software. Significance levels are presented as direct probabilities without correction for multiple comparisons. Associations between SLC6A3 genotype and smoking status were initially examined in Pearson chi-square tests and case-control odds ratio (OR) calculations on the complete data set. Associations after stratification of the data by protocol, sex, age, and ethnic group were examined via the Cochran-Mantel-Haenszel (CMH) chi-square test and the Breslow-Day (BD) test for homogeneity of ORs. The effects of the demographic variables sex, age, ethnic group, and Kinsey score on the association between SLC6A3 genotype and smoking status were analyzed by logistic regression. Associations between SLC6A3 genotype and TCI scores were analyzed in one-way analyses of variance (ANOVAs) and corrected for demographic variables by inclusion as covariates. The within-family association test for TCI scores examined all sibling pairs discordant for SLC6A3-9 genotype (Benjamin et al., 1996; Lesch et al., 1996). The paired-sample t value was conservatively corrected for the nonindependence of sibling pairs from the same family, and significance values were calculated in a one-sided test because the hypothesized direction of

Table 1
Associations Between Dopamine Transporter (SLC6A3) Genotype and Smoking Status

Smoking status	SLC6A3 genotype			
	/		9/9 + 9/*	
	n	%	n	%
Overall				
Nonsmokers	335	56.5	258	43.5
Current smokers	164	58.0	119	42.0
Former smokers	111	48.1	120	51.9
χ^2 (2, N = 1,107)			6.03	
p			.049	
Smoking initiation				
Nonsmokers	335	56.5	258	43.5
Current + former smokers	275	53.5	239	46.5
χ^2 (1, N = 1,107)			0.99	
p			.318	
Smoking cessation				
Current smokers	164	58.0	119	42.0
Former smokers	111	48.1	120	51.9
χ^2 (1, N = 514)			5.01	
p			.025	

Note. An asterisk indicates an SLC6A3 allele other than 9.

the association was known in advance. Similar results were obtained when only one sibling pair from each family was evaluated.

Results

Association of SLC6A3 With Smoking Cessation

A VNTR sequence in the 3' untranslated region of the SLC6A3 gene was genotyped in our diverse population. On the basis of previous results (Lerman et al., 1999), the genotypes were dichotomized into those containing or lacking allele 9.

Table 1 (top) shows that the frequency of SLC6A3-9 genotypes was not random with regard to smoking status as determined by a chi-square test ($p = .049$). As a means of determining whether SLC6A3 is associated with the initiation or cessation of smoking behavior, the original 2×3 contingency table was broken down into the two relevant 2×2 tables: nonsmokers versus current and former smokers (to assay for initiation) and current versus former smokers (to assay for cessation). Table 1 shows that there was no association between the SLC6A3 genotype and smoking initiation ($p = .318$). By contrast, there was a significant association between SLC6A3 and smoking cessation ($p = .025$). Specifically, 51.9% of former smokers and 42.0% of current smokers had an SLC6A3-9 genotype. A case-control OR calculation showed that participants with SLC6A3-9 genotypes were approximately 1.5 times more likely to have quit smoking than were subjects without allele 9 ($OR_{cessation} = 1.49$, 95% confidence interval [CI] = 1.05–2.11).

Because the study population was composed of participants from three different protocols with different sample sizes and proportions of current and former smokers, it was important to examine the association between SLC6A3 genotype and smoking cessation after stratification of the data by protocol. This analysis showed that there was a trend for a positive association between SLC6A3-9 and smoking cessation in participants from each of the three populations included in the study: (a) cancer-risk-related behaviors, $\chi^2(1, N = 104) = 4.86, p = .027, OR_{cessation} = 3.28, 95\% CI = 1.10-9.77$; (b) personality genetics, $\chi^2(1, N = 127) = 1.41, p = .235, OR_{cessation} = 1.55, 95\% CI = 0.75-3.19$; and (c) sexual behavior, $\chi^2(1, N = 283) = 2.50, p = .113, OR_{cessation} = 1.46, 95\% CI = 0.91-2.34$. A Cochran-Mantel-Haenszel analysis of the stratified data showed that the association between SLC6A3-9 and smoking cessation was as significant as or more significant than that in the pooled data, $\chi^2 = 7.04, p = .008, OR_{cessation} = 1.65, 95\% CI = 1.14-2.38$. Furthermore, a Breslow-Day test showed no evidence for heterogeneity of the ORs among protocols, $\chi^2_{BD}(2) = 1.84, p = .399$.

The association between SLC6A3-9 and smoking cessation remained significant after correction for sex, age, ethnic group, and Kinsey score by logistic regression, $\chi^2_{Wald}(1, N = 514) = 3.94, p = .047$. Stratification of the data by ethnic group showed that the association was significant when only White non-Hispanic participants were considered, $\chi^2(1, N = 450) = 4.44, p = .035, OR_{cessation} = 1.49, 95\% CI = 1.03-2.17$. Although the individual minority populations were too small to reveal significant effects of SLC6A3, there was a clear trend in the expected direction in the African American-Black participants, for whom the most data were available, $\chi^2(1, N = 25) = 3.11, p = .078, OR_{cessation} = 6.88, 95\% CI = 0.67-70.80$. Cochran-Mantel-Haenszel analysis of the ethnic-group-stratified data produced a significant result, $\chi^2_{CMH} = 4.92, p = .027, OR_{cessation} = 1.50, 95\% CI = 1.05-2.13$, and there was no evidence for heterogeneity of the ORs, $\chi^2_{BD}(4) = 4.45, p = .349$.

SLC6A3 genotype had a stronger effect on smoking cessation in men, $\chi^2(1, N = 244) = 6.50, p = .011, OR_{cessation} = 1.94, 95\% CI = 1.16-3.22$, than in women, $\chi^2(1, N = 270) = 0.36, p = .547, OR_{cessation} = 1.16, 95\% CI = 0.71-1.88$; however, this difference did not reach statistical significance, $\chi^2_{BD}(1) = 2.03, p = .154$. Cochran-Mantel-Haenszel analysis of the sex-stratified data produced a significant result, $\chi^2_{CMH} = 4.83, p = .028, OR_{cessation} = 1.48, 95\% CI = 1.04-2.10$. The effects of age on the association between SLC6A3 genotype and smoking cessation were tested by stratifying the data into age quartiles (18–21, 22–31, 32–41, and 42–84 years). Cochran-Mantel-Haenszel analysis of the age-matched data produced an OR similar to that observed for the total data set, $\chi^2_{CMH} = 3.69, p = .055, OR_{cessation} = 1.42, 95\% CI = 0.99-1.39$, and there was no significant evidence for heterogeneity of the ORs across age groups, $\chi^2_{BD}(3) = 1.44, p = .696$. These results provide evidence that the association between SLC6A3-9 genotypes and smoking cessation was not due to confounding effects of study population, race, or demographic variables.

Table 2
Associations Between Dopamine Transporter (SLC6A3) Genotype and Personality Traits

Personality trait	Personality trait score				<i>F</i> (1, 513) ^a	<i>d</i> ^b	<i>p</i>
	/		9/9 + 9/*				
	(n = 265)		(n = 250)				
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
Novelty seeking	21.59	6.75	20.22	6.42	5.54	-0.21	.019
Harm avoidance	13.02	7.46	13.61	7.04	0.87	<i>ns</i>	<i>ns</i>
Reward dependence	16.95	4.09	16.85	4.30	0.07	<i>ns</i>	<i>ns</i>
Persistence	5.31	1.96	5.38	2.00	0.72	<i>ns</i>	<i>ns</i>

Note. An asterisk indicates an SLC6A3 allele other than 9.

^aOne-way analysis of variance. ^b(Mean 2 - Mean 1)/*SD*.

Because many of the study participants were genetically related, it was important to show that the observed association between SLC6A3-9 and smoking cessation was not dependent on correlations between family members. This was demonstrated by analyzing a single, arbitrarily chosen member of each family, which produced an OR for smoking cessation that was indistinguishable from that observed for the complete data set, $\chi^2(1, N = 309) = 3.38, p = .066$, $OR_{cessation} = 1.53, 95\% CI = 0.97-2.40$, and was statistically significant after stratification of the data by protocol, $\chi^2_{CMH} = 5.14, p = .023, OR_{cessation} = 1.74, 95\% CI = 1.08-2.81$. Although the motivation for using families with sibling pairs was to perform within-family association analyses, the current data set lacked sufficient power to conduct a statistically meaningful test. Specifically, only sibling pairs that are discordant for both genotype and phenotype are highly informative for a dichotomous variable such as cigarette smoking; however, there were only 12 such pairs available, which was too small a sample for analysis. Interestingly, of these 12 sibling pairs, there were 8 pairs in which the former smoker carried allele 9 and 4 pairs in which the current smoker carried allele 9. Thus, the sibling pair analysis (albeit not statistically significant) supported the population association results.

Role of Novelty Seeking

The possible role of personality traits in the association between the SLC6A3 gene and smoking behavior was tested via the TCI (Cloninger et al., 1994). Table 2 shows that of the four TCI temperamental factors, SLC6A3 was associ-

ated only with novelty seeking, a trait previously predicted to be influenced by dopamine (Cloninger, 1994; Cloninger et al., 1993). The average novelty seeking score for participants with SLC6A3-9 genotypes was 1.37 points lower than for participants without allele 9, a difference of 0.21 standard deviation units ($p = .019$). The association between SLC6A3 and novelty seeking remained significant when sex, age, ethnic group, and Kinsey score were included as covariates in the ANOVA, $F(1, 515) = 4.87, p = .028$.

The association between SLC6A3 and novelty seeking was further examined in a within-family test designed to distinguish between genetic transmission and population stratification (Benjamin et al., 1996; Lesch et al., 1996). Fifty sibling pairs from 39 families were discordant for SLC6A3-9 genotypes and had available TCI test scores. A paired *t* test showed that the participants with allele 9 scored 2.3 points lower on novelty seeking than did their siblings without allele 9, a significant difference (average score for SLC6A3-9⁻ genotypes: 21.7, *SD* = 5.8; average score for SLC6A3-9⁺ genotypes: 19.4, *SD* = 6.7), $t(49) = 1.86, p = .035$. Hence, the effect of SLC6A3 genotype was as strong within sibships as it was in the total population. None of the other TCI traits showed a significant association with SLC6A3 via this test.

Because SLC6A3 allele 9 was associated positively with smoking cessation but negatively with novelty seeking, we hypothesized that low novelty seeking would be a predictor of smoking cessation. This idea was tested by comparing personality test scores in current and former smokers. Table 3 shows that average novelty seeking scores were

Table 3
Associations Between Personality Traits and Smoking Cessation

Personality trait	Personality trait score				<i>F</i> (1, 244) ^a	<i>d</i> ^b	<i>p</i>
	Current smokers		Former smokers				
	(n = 148)		(n = 98)				
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
Novelty seeking	22.95	6.62	19.33	5.98	19.07	-0.55	.00002
Harm avoidance	13.83	7.63	13.00	7.29	0.74	<i>ns</i>	<i>ns</i>
Reward dependence	16.84	4.20	17.38	3.92	1.03	<i>ns</i>	<i>ns</i>
Persistence	4.91	2.09	5.33	1.77	2.87	<i>ns</i>	<i>ns</i>

^aOne-way analysis of variance. ^b(Mean 2 - Mean 1)/*SD*.

indeed 3.6 points lower in former smokers than in current smokers, a difference of 0.55 standard deviation units ($p < .0001$). None of the other personality factors measured by the TCI were significantly associated with smoking cessation.

DRD2 Results

The dopamine D_2 receptor Taq1 polymorphism, DRD2-A1/A2, was genotyped in 738 of the participants. The frequencies of A1 genotypes (A1/A1 and A1/A2) were 41.1% for nonsmokers, 49.4% for current smokers, and 39.8% for former smokers, $\chi^2(2, N = 738) = 3.91, p = .141$. Among participants with DRD2-A1 genotypes, the frequencies of SLC6A3-9 genotypes were 40.2% in nonsmokers, 37.2% in current smokers, and 38.9% in former smokers, $\chi^2(2, N = 314) = .21, p = .899$; among participants with the DRD2-A2/A2 genotype, the frequencies of SLC6A3-9 genotypes were 44.7% in nonsmokers, 43.8% in current smokers, and 57.8% in former smokers, $\chi^2(2, N = 424) = 5.81, p = .054$.

Discussion

The main effect of the SLC6A3 gene in our sample was on smoking cessation; individuals carrying the SLC6A3-9 allele were 1.5-fold more likely to have quit smoking than were individuals lacking this polymorphism. This result supports Lerman et al.'s (1999) finding of an association between SLC6A3 and length of previous cessation attempts in current smokers. However, the two studies diverge in that we did not find a significant difference in SLC6A3-9 genotypes between nonsmokers and current smokers, nor did we find an effect on age of smoking initiation. There are several possible reasons for these discrepancies, including differences in the age, gender composition, and recruitment of the study populations. Thus, although both our study and that of Lerman et al. (1999) showed that SLC6A3-9 is associated with not smoking, further studies are required to determine whether this is due to effects on initiation, cessation, or both and whether the effects of the gene are variable across cohorts.

Analysis of TCI scores suggested that SLC6A3 mediates smoking behavior, at least in part, through the personality trait of novelty seeking. The SLC6A3-9 allele was associated with low novelty seeking, which in turn was associated with smoking cessation. Novelty seeking was previously postulated to be modulated by dopamine transmission (Cloninger, 1994; Cloninger et al., 1993).

Comings et al. (1996a) and Spitz et al. (1998) have previously reported associations between smoking behavior and a different dopaminergic gene, the D_2 receptor locus, whereas Lerman et al. (1999) found a gene-gene interaction between DRD2 and SLC6A3. In agreement with these studies, we found that DRD2-A1 genotypes were increased in smokers, whereas the association between SLC6A3 and smoking behavior was stronger in DRD2-A2 genotypes. However, neither trend was significant in our data set, suggesting that DRD2 has a weaker effect than SLC6A3 and

may act as a modifier locus. Previous studies have also found an association between the dopamine D_4 receptor gene and measures of novelty seeking (Benjamin et al., 1996; Ebstein et al., 1996). However, we have not found an association between the D4DR gene and smoking behavior, perhaps because the D_4 receptor influences different facets of novelty seeking than does the dopamine transporter.

Previous studies have shown that the 9-repeat allele of the SLC6A3 gene is associated with cocaine-induced paranoia, which has been attributed to high dopamine (Gelernter et al., 1994), whereas the 10-repeat allele is associated with attention deficit disorder (Cook et al., 1995) and Tourette's syndrome (Comings et al., 1996b), two conditions attributed to low dopamine neurotransmission. This suggests that SLC6A3-9 may increase dopamine signaling, perhaps by reducing dopamine transporter protein expression through an effect on mRNA processing or stability; however, this must be regarded as speculation until a biological effect of the SLC6A3-9 allele, or another polymorphism in linkage disequilibrium with it, has been demonstrated.

The role of dopamine in novelty seeking personality traits and the rewarding effect of external stimuli, including drugs, have been demonstrated by genetic and pharmacological experiments (Cloninger, 1994; Wise & Rompre, 1989). For example, it has been shown in mice that exploratory behavior, the closest animal analog to novelty seeking, is reduced by manipulations that decrease dopamine transmission and increased by manipulations that raise dopamine signaling (Fink & Smith, 1980; Zhou & Palmiter, 1995). In humans, novelty seeking is specifically decreased in dopamine-deficient patients with Parkinson's disease (Menza, Golbe, et al., 1993). It has also been shown that many different addictive drugs activate dopamine release in the nucleus accumbens (Di Chiara & Imperato, 1988; Koob, 1992) and that dopaminergic drugs reduce the intake of some of these substances (Caine & Koob, 1993).

In addition, the idea that differences in novelty seeking and responsiveness to external stimuli can influence smoking behavior is supported by both the present data and previous studies. Pomerleau et al. (1992) reported that novelty seeking was higher in smokers than in nonsmokers but was not related to measures of nicotine dependence. Heath et al. (1995) found the highest levels of novelty seeking in current smokers, the lowest levels in nonsmokers, and intermediate levels in former smokers. Menza, Forman, Sage, and Golbe (1993) studied Parkinson's disease patients, who have lower smoking rates than the general population, and showed that those who did smoke had the highest novelty seeking scores. Cigarette smoking has also been associated with Zuckerman's Sensation Seeking Scale, an independent measure of novelty seeking personality (Zuckerman, 1994). An alternative hypothesis, that high novelty seeking is caused by cigarette smoking, seems unlikely because longitudinal studies have shown that differences in traits resembling novelty seeking precede rather than follow changes in smoking status (Barefoot et al., 1989; Lipkus et al., 1994).

The hypothesis that the dopamine transporter gene influences smoking behavior through novelty seeking could

explain why we observed a difference in SLC6A3 allele frequencies in current versus former smokers, whereas Lerman et al. (1999) observed a difference in nonsmokers versus current smokers. The reason is that novelty seeking is associated with both smoking cessation ($R = -.269$, $R^2 = .073$; see Table 3) and, in the opposite direction, smoking initiation ($R = .084$, $R^2 = .007$; see also Heath et al., 1995). Thus, high novelty seekers are both more likely to start smoking and less likely to quit smoking than are low novelty seekers.

Although allelic association is a powerful method for detecting quantitative genetic influences on complex traits such as cigarette smoking, there are limitations to such studies. First, it is not yet clear whether the association with SLC6A3-9 is due to a direct effect of this 3' untranslated region polymorphism on the expression of the dopamine transporter gene or to linkage disequilibrium with some other polymorphism. Second, allelic association can arise as a result of population stratification as well as genuine transmission. Although we were able to rule out population stratification as a reason for the association to novelty seeking in a within-family test, the data set was not large enough to perform a similar analysis of smoking status. Third, and most important, the effect size of the SLC6A3 gene is small, accounting for less than 2% of the total variance in both smoking behavior and personality traits. Thus, the dopamine transporter gene is only one of many different factors, both genetic and environmental, that influence smoking behavior.

Clearly, the dopamine transporter locus cannot be a "cigarette smoking gene" in any specific sense because it evolved long before the introduction of tobacco to human populations. Nor should the dopamine transporter gene be regarded as a strict determinant of the ability to quit smoking, because nearly half of former smokers lacked the protective polymorphism. Rather, we envision that variations in the dopamine transporter gene influence an individual's general need and responsiveness to external stimuli, of which cigarette smoking is but one example. Current smoking cessation programs treat all smokers the same. Perhaps a fuller understanding of the genetics of cigarette smoking behavior will lead to more effective, targeted pharmacological and psychoeducational cessation strategies that take such individual differences into account.

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