

Evidence Suggesting the Role of Specific Genetic Factors in Cigarette Smoking

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Twin studies suggest that propensity to smoke and ability to quit smoking are influenced by genetic factors. As a means of investigating the risk of smoking associated with genetic polymorphisms in the dopamine transporter (SLC6A3) and the D₂ dopamine receptor (DRD2) genes, a case-control study of 289 smokers and 233 nonsmoking controls and a case series analysis of smokers were conducted. A significant effect for SLC6A3 and a significant gene-gene interaction were found in a logistic regression model, indicating that individuals with SLC6A3-9 genotypes were significantly less likely to be smokers, especially if they also had DRD2-A2 genotypes. Smokers with SLC6A3-9 genotypes were also significantly less likely to have started smoking before 16 years of age and had prior smoking histories indicating a longer period of prior smoking cessation. This study provides preliminary evidence that the SLC6A3 gene may influence smoking initiation and nicotine dependence.

Key words: dopamine, genetics, smoking

Despite more than a decade of intensive smoking prevention and treatment efforts, about 26% of Americans 17 years old and older continue to smoke (Centers for Disease

Control, 1996). Twin studies indicate that inherited factors account for as much as 50% of the variance in cigarette smoking practices (Carmelli, Swan, Robinette, & Fabsitz, 1992; Heath & Martin, 1993). Several converging lines of evidence point to the neurotransmitter dopamine as a possible explanation for these genetic effects (Carr, Basham, York, & Rowell, 1992; Di Chiara & Imperato, 1988; Henningfield, Schuh, & Jarvik, 1995; Pontieri, Tanda, Orzi, & Di Chiara, 1996). As with other psychostimulants, the reinforcing properties of nicotine have been attributed to nicotine's effects on dopamine transmission (Di Chiara & Imperato, 1988; Henningfield et al., 1995) and, specifically, its effects on the D₂ receptor (O'Neill, Dourish, & Iversen, 1991). Nicotine has been shown to stimulate dopamine release (Di Chiara & Imperato, 1988) and to inhibit reuptake (Carr et al., 1992), thereby increasing levels of synaptic dopamine and satisfying the reward mechanism (Dani & Heinemann, 1996; Wise & Rompre, 1989).

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This research was supported in part by grants from the National Cancer Institute (RO1 CA63562) and the Department of Defense (D17-95-1-5022).

We would like to thank Chris Borillo, Anna Ryan Robertson, Irene Angel, and Susan Marx for their assistance with data collection and report preparation; Margie Clapper and David Schaebler for their help with sample preparation; Tracy Orleans for her input on measurement; Terri Lehman and Bioserve Biotechnologies (Laurel, Maryland) for their technical expertise; Joel Gelernter, David Comings, and David Flockhart for their review and very helpful comments on this article; Bruce Trock for his input into the analytic strategy; and Curtis C. Harris for his insightful discussions.

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Genetic variation in the dopamine receptor (DRD2) gene and the dopamine transporter gene (SLC6A3) may influence concentrations of and responses to synaptic dopamine. There is laboratory and epidemiological evidence to implicate these genes in a variety of disorders. The DRD2-A1 allele has been associated with a reduced density of dopamine receptors (Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991). In comparison with persons with DRD2-A2 genotypes, those with DRD2-A1 genotypes (A1/A1 or A1/A2) were found to be more likely to exhibit compulsive and addictive behaviors (Blum et al., 1990; Comings, Ferry,

et al., 1996; Comings, Wu, et al., 1996; Noble et al., 1994). However, the results of several reports have been inconsistent (Goldman et al., 1994). By contrast, the SLC6A3 gene regulates synaptic dopamine by coding for a reuptake protein called the dopamine transporter (DAT; Bannon, Granneman, & Kapatos, 1995). This gene has been implicated in Parkinson's disease (Seeman & Niznik, 1990), attention deficit disorder (Cook et al., 1995), and Tourette's syndrome (Comings, Wu, et al., 1996). SLC6A3 has a 3' variable number tandem repeat (VNTR; 40 base pair [bp]) polymorphism or variation within the population (Vandenberg et al., 1992). The 9-repeat allele (variant of the gene) has been associated with cocaine-induced paranoia, a state attributed to diminished dopamine reuptake and greater availability of synaptic dopamine (Gelernter, Kranzler, Sattel, & Rao, 1994).

On the basis of these reports, we predicted that the SLC6A3-9 and DRD2-A2 genotypes would be associated with a reduced risk of cigarette smoking because of the greater availability of synaptic dopamine and functioning receptors, respectively. To test this hypothesis, we performed a case-control study of smokers (cases) and nonsmokers (controls). In a previous report, we examined the association of the dopamine D4 receptor gene with smoking practices among smokers. The present study extended this line of research by testing and evaluating the association of two additional genes with smoking status using case-control methodology.

Method

Participants

Participants were 289 smokers who reported smoking at least 5 cigarettes per day for at least 1 year and 233 never smokers (controls) who reported having smoked fewer than 100 cigarettes in their lifetimes (hereafter referred to as "nonsmokers"). Exclusion criteria were as follows: less than 18 years of age, personal history of cancer, undergoing treatment for drug or alcohol addiction, or presence of a psychiatric disorder that precluded informed consent. Among nonsmoking participants, those with carbon monoxide levels in exhaled air of 8 ppm or higher (indicative of current smoking) were excluded from the study. Subsets of these smoker and nonsmoker samples were also examined in previous reports of the dopamine D4 receptor gene and the tyrosine hydroxylase gene (Lerman et al., 1998; Lerman, Shields, et al., 1997).

Procedure

Smoking participants were recruited through varied newspaper advertisements and flyers inviting them to participate in a free smoking cessation program (see Lerman, Gold, et al., 1997). Nonsmoking participants were recruited through similar mechanisms for a study of factors influencing smoking. They were paid \$25 to defray the costs of transportation.

All participants donated blood for analysis. DNA was extracted from whole blood or buffy coats via a standard phenolchloroform extraction method. For SLC6A3 genotyping, DNA (25 ng) was mixed with primers (20 pmol), GeneAmp PCR buffer (10 mM tris-HCl pH 8.3, 50 mM KCl, 1.5 mM MgCl₂, and 0.0001% gelatin; Perkin Elmer, Norwalk, CT), Amplitaq DNA polymerase (2.5 μ

Perkin Elmer, Norwalk, CT), and 2'-deoxynucleotides-3'-triphosphates (144 μM; Pharmacia, Piscataway, NJ) in 50-μl total volume. The reaction conditions included an initial melting step (94 °C; 4 min) followed by 35 cycles of melting (94 °C; 1 min), annealing (65 °C; 1 min), and extending (72 °C; 1 min). The VNTR repeat was determined with a 4% agarose gel electrophoresis (3:1 nusieve:agarose). For the DRD2-A1 genetic polymorphism, DNA (60 ng) was mixed with primers (50 pmol), buffer (Gibco BRL), MgCl₂ (2.5 mM), Amplitaq DNA polymerase (2.5 μ; Perkin Elmer, Norwalk, CT), and 2'-deoxynucleotides-3'-triphosphates (150 μM; Pharmacia, Piscataway, NJ) in a final volume of 100 μl. The reaction conditions included an initial melting step (94 °C; 5 min) followed by 35 cycles of melting (94 °C; 1 min), annealing (58 °C; 1 min), and extending (72 °C; 1 min). A final extension step was used (72 °C; 5 min). An aliquot (25 μl) was then subjected to TaqI restriction fragment length polymorphism (RFLP) digestion according to the manufacturer's instructions. The final bands (310 bp for the A1 allele and 180 bp plus 130 bp for the A2 allele) were determined via agarose (1%) gel electrophoresis. In all assays, 20% of the samples were repeated for quality control. All gels were read independently by two investigators.

Measures

Participants completed a self-report questionnaire measure of demographic characteristics, smoking history (age at smoking initiation and length of previous quitting periods), height, weight, medication use, and alcohol intake (Lerman, Gold, et al., 1997). The Fagerstrom test for nicotine dependence, a six-item self-report measure, was also administered. This instrument was derived from the Fagerstrom Tolerance Questionnaire (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991).

Statistical Analysis

DRD2 genotype was classified as the presence or absence of the A1 allele (A1/A1 or A1/A2 vs. A2/A2). (Each individual has two "alleles" or gene copies; these two copies are the "genotype.") This was consistent with previous studies showing associations of the A1 allele (in heterozygous or homozygous form) with addictive and compulsive behaviors (Blum et al., 1990; Comings, Ferry, et al., 1996). SLC6A3 genotype was classified as the presence or absence of the 9 allele (9/9 or 9/* vs. */*, where * refers to alleles other than 9). This was consistent with previous research relating the SLC6A3-9 allele with cocaine-induced paranoia, a state attributed to excess dopamine (Gelernter et al., 1994). Other reports have examined the prevalence of the SLC6A3-10 allele; however, more than 80% of our participants had at least one 10 allele, resulting in a very skewed distribution. Therefore, analyses of SLC6A3 were based on the presence or absence of the 9 allele.

Associations between genotype and smoking, along with possible interacting effects of SLC6A3 and DRD2, were initially examined in chi-square tests of association. Caucasians and African Americans were examined separately as a result of ethnic differences in allele frequencies. Associations of genotype with continuous smoking variables (e.g., length of prior quitting period) were examined via *t* tests. The main and interacting effects of the SLC6A3 and DRD2 genotypes were then examined in logistic and linear regression analyses controlling for potential confounder variables (age, gender, education, race, body mass index, alcohol intake [number of drinks of beer, wine, or hard liquor per week], and current use of psychotropic medication). Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by uncondi-

tional logistic regression using SAS. All *p* values reported are two-sided.

Results

Descriptive Data

The sample included 289 smokers and 233 nonsmokers 18–80 years of age ($M \pm SD = 43 \pm 11$ years), 42% of whom were male and 58% of whom were female. The racial composition was 85% Caucasian ($n = 444$) and 15% African American ($n = 78$). Demographic characteristics of the smoker and nonsmoker groups are shown in Table 1. Among smokers, the average smoking rate was 22 ± 10 cigarettes per day, and the average age of initiation of smoking was 17 ± 4 years.

The allelic and genotype frequencies for SLC6A3 were similar to those reported in the literature (Table 2; Doucette-Stamm, Blakely, Tian, Mockus, & Mao, 1995; Gelernter et al., 1994). The allelic and genotype frequencies for the DRD2 gene were also similar to previous reports (Table 3; Bolos et al., 1990). The SLC6A3-9 genotype (9/9 or 9/*) was significantly less common in African Americans than in Caucasians (32% vs. 54%), $\chi^2(1, N = 522) = 12.85$, $p = .001$. The DRD2-A1 genotype (A1/A1 or A1/A2) was significantly more common in African Americans than in Caucasians (48% vs. 35%), $\chi^2(1, N = 522) = 5.24$, $p = .02$. The distribution of DRD2 and SLC6A3 genotypes was consistent with Hardy-Weinberg equilibrium for Caucasians and African Americans.

Associations of SLC6A3 and DRD2 With Smoking Risk

As shown in Table 4, smokers were significantly less likely to have SLC6A3-9 genotypes (46.7%) than were nonsmokers (55.8%), $\chi^2(1, N = 522) = 4.26$, $p = .04$. Among Caucasians, fewer smokers than nonsmokers had SLC6A3-9 genotypes, $\chi^2(1, N = 444) = 3.02$, $p = .08$.

Table 1
Demographic Characteristics and Alcohol and Medication Use by Study Group

Variable	Level	Smokers		Nonsmokers	
		<i>n</i>	%	<i>n</i>	%
Age** (years)	18–29	32	11.1	58	24.9
	30–49	180	62.3	96	41.2
	50+	77	26.6	79	33.9
Gender	Male	121	41.9	96	41.2
	Female	168	58.1	137	58.8
Education*	High school or less	40	13.9	18	7.7
	More than high school	246	86.1	215	92.3
Race*	Caucasian	237	82.0	207	88.8
	African American	52	18.0	26	11.2
Alcohol use	Yes	127	43.9	118	50.6
	No	162	56.1	115	49.4
Psychotropic medications**	Yes	50	17.3	9	3.9
	No	239	82.7	224	96.1

* $p < .05$. ** $p < .001$.

Table 2
Dopamine Transporter (SLC6A3) Genotypes and Allele Frequencies in Combined Samples of Smokers and Nonsmokers

Allele or genotype	Caucasians		African Americans	
	<i>n</i>	%	<i>n</i>	%
Allele				
3 ⁻	0	0.0	5	3.2
6	18	2.0	2	1.3
7	1	0.1	0	0.0
8	3	0.3	3	1.9
9	280	31.5	30	19.2
10	577	65.0	114	73.1
11	9	1.0	2	1.3
Total	888		156	
Genotype				
6/6	7	1.6	1	1.3
9/3	0	0.0	1	1.3
9/6	1	0.2	0	0.0
9/7	1	0.2	0	0.0
9/8	1	0.2	1	1.3
9/9	40	9.0	5	6.4
10/3	0	0.0	4	5.1
10/6	3	0.7	0	0.0
10/8	2	0.5	2	2.6
10/9	195	43.9	18	23.1
10/10	187	42.1	45	57.7
11/9	2	0.5	0	0.0
11/10	3	0.7	0	0.0
11/11	2	0.5	1	1.3
Total	444		78	

However, there were no differences between Caucasian smokers and nonsmokers in the prevalence of DRD2 genotypes. Associations of SLC6A3 and DRD2 genotypes with smoking were not evident in African Americans.

This association of SLC6A3 with smoking was modified by DRD2 genotype (Figure 1). Among Caucasian participants with DRD2-A2 genotypes, 62% of nonsmokers had SLC6A3-9 genotypes, as compared with 46% of smokers, $\chi^2(1, N = 288) = 7.01$, $p = .008$. Among those with DRD2-A1 genotypes (A1/A1 or A1/A2), SLC6A3 genotype was not associated with smoking, $\chi^2(1, 156) = 0.44$, $p =$

Table 3
D₂ Dopamine Receptor (DRD2) Genotypes and Allele Frequencies in Combined Samples of Smokers and Nonsmokers

Allele or genotype	Caucasians		African Americans	
	<i>n</i>	%	<i>n</i>	%
Allele				
A1	171	19.3	47	30.1
A2	717	80.7	109	69.9
Total	888		156	
Genotype				
A1/A1	15	3.4	9	11.5
A1/A2	141	31.8	29	37.2
A2/A2	288	64.9	40	51.3
Total	444		78	

Table 4
Associations of Dopamine Transporter (SLC6A3)
and D₂ Dopamine Receptor (DRD2) Genotypes With Smoking

Sample	Group	SLC6A3 genotype				DRD2 genotype			
		9/9 + 9/*		*/*		A1/A1 + A1/A2		A2/A2	
		n	%	n	%	n	%	n	%
All participants (n = 522)	Smokers	135	46.7	154	53.3	113	39.1	176	60.9
	Controls	130	55.8	103	44.2	81	41.7	152	46.3
		$\chi^2(1, 522)$		4.26				1.04	
		p		.04				.31	
Caucasians (n = 444)	Smokers	119	50.2	118	49.8	88	37.1	149	62.8
	Controls	121	58.4	86	41.6	68	32.8	139	67.1
		$\chi^2(1, 444)$		3.02				0.89	
		p		.08				.35	
African Americans (n = 78)	Smokers	16	30.8	36	69.2	25	48.1	27	51.9
	Controls	9	34.6	17	65.4	13	50.0	13	50.0
		$\chi^2(1, 78)$		0.12				0.03	
		p		.73				.87	

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

.51. A similar but nonsignificant association with SLC6A3 was observed in African American participants; among those with DRD2-A2 genotypes, 46% of nonsmokers had SLC6A3-9 genotypes, as compared with 22% of smokers (Fisher's test, $p = .15$). Among those with DRD2-A1 genotypes, SLC6A3 genotype was not associated with smoking (Fisher's test, $p = .47$).

To rule out the effects of potential confounder variables, we tested the DRD2 and SLC6A3 main effects and their interaction in a logistic regression model controlling for the confounder variables identified in Table 1 (race, education, age, and medication use). The SLC6A3 main effect was statistically significant (OR = 0.52, 95% CI = 0.32–0.82, $p = .006$), as was the DRD2 \times SLC6A3 interaction term (OR = 2.65, 95% CI = 1.23–5.70, $p = .01$). There was no significant main effect of DRD2 (OR = 0.71, 95% CI = 0.41–1.23).

Associations of SLC6A3 and DRD2 With Smoking Variables

Among smokers, we also examined the associations of SLC6A3 and DRD2 genotypes with age at smoking initiation and quitting history. There were significant associations of the SLC6A3 genotype with age at initiation of smoking; 26% of smokers with SLC6A3-9 genotypes started smoking before 16 years of age, as compared with 37% of smokers with other SLC6A3 genotypes, $\chi^2(1, N = 288) = 3.91, p = .05$. This effect remained significant in a logistic regression model controlling for race, education, age, and use of psychotropic medications (OR = 0.58, 95% CI = 0.34–0.99, $p = .05$).

Smokers with SLC6A3-9 genotypes also reported having quit previously for a significantly longer period than those with other genotypes (471.9 \pm 93.9 days vs. 229.5 \pm 42.3

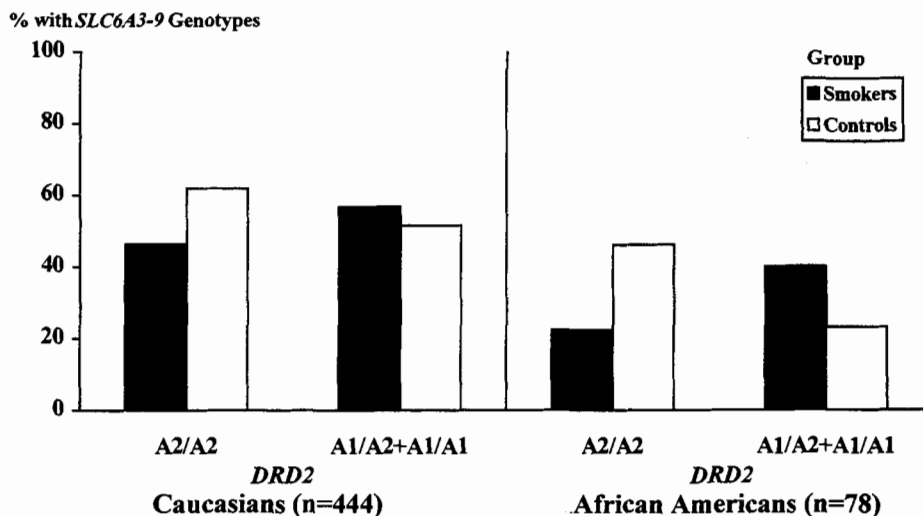


Figure 1. Percentages of smokers and controls with dopamine transporter 9 (SLC6A3-9) genotypes by D₂ dopamine receptor (DRD2) genotypes and race.

days), $t(183) = 2.35$, $p = .02$. This effect remained significant in a linear regression model controlling for race, education, age, and use of psychotropic medications, $F(5, 274) = 6.01$, $p = .02$. The DRD2 genotype was not associated with age at smoking initiation, $\chi^2(1, N = 288) = 2.2$, $p = .13$, or quitting history, $t(281) = 0.24$, $p = .81$. The SLC6A3 \times DRD2 interaction term was not significant. There were no associations of these genotypes with nicotine dependence level.

Discussion

This study provides the first evidence that the dopamine transporter (SLC6A3) genotype is associated with smoking risk, age at smoking initiation, and ability to quit smoking. Furthermore, the association with smoking risk was modified by the dopamine receptor (DRD2) genotype, resulting in a 50% reduction in smoking risk for individuals with SLC6A3-9 and DRD2-A2 genotypes. This finding is consistent with the results of Hamer and colleagues (Sabol et al., 1999) showing a higher prevalence of SLC6A3-9 repeat genotypes among former smokers than among current smokers; however, these authors did not replicate the modifying effects of DRD2. Nonetheless, on the basis of the epidemiological evidence, a biological mechanism for our findings can be postulated. Because nicotine stimulates brain reward centers via dopaminergic pathways, previous studies of disorders relating to either increased or decreased dopamine are relevant. First, dopamine transporter (DAT), the protein product of SLC6A3, has been associated with Parkinson's disease (Seeman & Niznik, 1990). This condition is related to decreased synaptic dopamine, and nicotine has been shown to have protective effects (Newhouse & Hughes, 1991). Second, the SLC6A3-9-repeat allele has been associated with cocaine-induced paranoia (Gelernter et al., 1994), a state attributed to excess dopamine. The SLC6A3-10-repeat allele, the other common allele, has been associated with attention deficit disorder (Cook et al., 1995) and Tourette's syndrome (Comings, Wu, et al., 1996), two conditions attributed to insufficient dopamine. Thus, the SLC6A3-9 allele might be associated with increased synaptic dopamine (and the 10 allele with decreased dopamine). Individuals with SLC6A3-9 genotypes and higher levels of endogenous synaptic dopamine should therefore have less need to use exogenous substances such as nicotine to stimulate dopamine transmission. Moreover, because the DRD2-A1 allele has been related to a reduced density of D₂ receptors (Noble et al., 1991), this protective effect of SLC6A3-9 (and increased synaptic dopamine) on smoking behavior may be especially pronounced in persons with DRD2-A2 genotypes (who have normal receptor density). In other words, the availability of synaptic dopamine may decrease the need for nicotine only if there are sufficient receptors for normal dopamine transmission. It should be noted, however, that the lack of a confirmed quantitative biological effect of the SLC6A3 polymorphism makes these conclusions preliminary.

Although we found a statistically nonsignificant higher prevalence of the DRD2-A1 genotype in smokers than in

nonsmokers, we did not observe the same magnitude of difference as in a previous study conducted by Comings, Ferry, and colleagues (1996). In this study, the prevalence of DRD2-A1 was 26% in controls, as compared with 49% in smokers. However, although the controls in this previous study were screened for alcoholism, they did not exclude smokers. Additional studies are needed to clarify the associations of DRD2 to smoking.

Association studies examining candidate alleles can provide more useful information than genetic linkage studies when studying common traits that are influenced by multiple genes with small effects; however, there are some limitations to studies such as this (Goldman et al., 1994). First, it is possible that these associations of the SLC6A3 genotype with smoking are due to the effects of a third variable, such as alcohol intake (Blum et al., 1990) or psychotropic medications. In the study reported here, these variables were unlikely confounders, because the main and interacting effects of SLC6A3 and DRD2 were not altered when these variables were included in multivariate models. A second potential source of bias is ethnic differences in allelic frequencies that relate to smoking practices. Because we did not collect data on ethnic differences within racial groups, the Caucasian-African American stratification might not have entirely removed such bias. Although some data suggest that intra-Caucasian variation is not likely to be large (Doucette-Stamm et al., 1995), the existence of significant genetic heterogeneity could confound study results. This may be especially problematic in studies, such as ours, that examine gene-gene interactions, thereby inflating the likelihood of false-positive results. Third, it should also be noted that the recruitment of study participants responding to newspaper advertisements for smoking cessation or nonsmoking volunteers might generate a sample that is not representative of the general population. Such volunteer bias could potentially exacerbate bias caused by genetic variation in different ethnic groups. Fourth, although there was sufficient statistical power to evaluate genetic effects in Caucasians, further research is needed to evaluate these effects in a larger sample of African Americans. Fifth, although nonsmoking status in control participants was verified by carbon monoxide testing, biochemical verification was not performed for the smokers. Although misclassification of smokers is theoretically possible, it seems implausible that lifetime nonsmokers would both seek enrollment and counseling for smoking cessation and falsely identify themselves as smokers in a detailed questionnaire.

Finally, the case-control/candidate gene approach is complementary to family-based (twin, subpair, and whole genome searches) studies that may identify hereditary contributions to smoking. Both population-based (Gelernter, Goldman, & Risch, 1993) and family (Risch, 1990) approaches have limitations in the study of complex behavioral phenotypes, so cautious interpretation is warranted. Future research using diverse designs in well-defined populations with careful phenotype characterization will be critical to advancing understanding (Plomin, Owen, & McGuffin, 1994).

Despite these limitations, the present study and that of

Sabol et al. (1999) provide an important first step in research exploring the genetic basis of cigarette smoking. A better understanding of genetic, neuropharmacologic, and environmental determinants can lead to the development of improved prevention and treatment strategies tailored to the needs of individual smokers (Plomin, 1998). For example, smokers with genetically determined reductions in dopamine transmission may respond better than other smokers to pharmacologic therapy involving nicotine replacement, psychotropic medications, or both. Initial data suggest that bupropion hydrochloride, which has selective dopamine reuptake inhibitory effects, can boost smoking cessation rates significantly (Ferry et al., 1992; Hurt et al., 1997), and the Food and Drug Administration has recently approved bupropion for smoking cessation treatment. The SLC6A3 gene product also inhibits dopamine reuptake, and our findings suggest that smokers who have SLC6A3 genotypes that do not contain the 9-repeat allele may respond better to this form of therapy. In addition, data relating SLC6A3 genotype to age at smoking initiation suggest promising avenues for targeting smoking prevention efforts to high-risk youth. Although it would be premature to integrate genotyping into clinical smoking prevention or cessation treatment at the present time, the current data suggest that future research in this area would be very fruitful.

References

- Bannon, M. J., Granneman, J. G., & Kapatos, G. (1995). The dopamine transporter: Potential involvement in neuropsychiatric disorders. In F. E. Bloom & D. J. Kupfer (Eds.), *Psychopharmacology: The fourth generation of progress* (pp. 179–188). New York: Raven Press.
- Blum, K., Noble, E. P., Sheridan, P. J., Montgomery, A., Ritchie, T., Jagadeeswaran, P., Nogami, H., Briggs, A. H., & Cohn, J. B. (1990). Allelic association of human dopamine D₂ receptor gene in alcoholism. *Journal of the American Medical Association*, *263*, 2055–2060.
- Bolos, A. M., Dean, M., Lucas-Derse, S., Ramsburg, M., Brown, G. L., & Goldman, D. (1990). Population and pedigree studies reveal a lack of association between the dopamine D2 receptor gene and alcoholism. *Journal of the American Medical Association*, *264*, 3156–3160.
- Carmelli, D., Swan, G. E., Robinette, D., & Fabsitz, R. (1992). Genetic influence on smoking—A study of male twins. *New England Journal of Medicine*, *327*, 829–833.
- Carr, L. A., Basham, J. K., York, B. K., & Rowell, P. P. (1992). Inhibition of uptake of 1-methyl-4-phenylpyridinium ion and dopamine in striatal synaptosomes by tobacco smoke components. *European Journal of Pharmacology*, *215*, 285–287.
- Centers for Disease Control. (1996). Cigarette smoking among adults—United States, 1994. *Morbidity and Mortality Weekly Report*, *45*, 588–590.
- Comings, D. E., Ferry, L., Bradshaw-Robinson, S., Burchette, R., Chiu, C., & Muhleman, D. (1996). The dopamine D2 receptor (DRD2) gene: A genetic risk factor in smoking. *Pharmacogenetics*, *6*, 73–79.
- Comings, D. E., Wu, S., Chiu, C., Ring, R. H., Gade, R., Ahn, C., MacMurray, J. P., Dietz, G., & Muhleman, D. (1996). Polygenic inheritance of Tourette syndrome, stuttering, attention deficit hyperactivity, conduct, and oppositional defiant disorder: The additive and subtractive effect of the three dopaminergic genes—DRD2, D beta H, and DAT1. *American Journal of Medical Genetics*, *67*, 264–288.
- Cook, E. H., Jr., Stein, M. A., Krasowski, M. D., Cox, N. J., Olkon, D. M., Kieffer, J. E., & Leventhal, B. L. (1995). Association of attention-deficit disorder and the dopamine transporter gene. *American Journal of Human Genetics*, *56*, 993–998.
- Dani, J. A., & Heinemann, S. (1996). Molecular and cellular aspects of nicotine abuse. *Neuron*, *16*, 905–908.
- Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences, USA*, *85*, 5274–5278.
- Doucette-Stamm, L. A., Blakely, D. J., Tian, J., Mockus, S., & Mao, J. I. (1995). Population genetic study of the human dopamine transporter gene (DAT1). *Genetic Epidemiology*, *12*, 303–308.
- Ferry, L. H., Robbins, A. S., Scariati, P. D., Burchette, R. J., Masterson, G. A., & Abbey, D. E. (1992). Enhancement of smoking cessation using the anti-depressant bupropion hydrochloride [Abstract]. *Circulation*, *86*, 671.
- Gelernter, J., Goldman, D., & Risch, N. (1993). The A1 allele at the D2 dopamine receptor gene and alcoholism: A reappraisal. *Journal of the American Medical Association*, *269*, 1673–1677.
- Gelernter, J., Kranzler, H. R., Satel, S. L., & Rao, P. A. (1994). Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. *Neuropsychopharmacology*, *11*, 195–200.
- Goldman, D., Brown, G. L., Albaugh, B., Robin, R., Goodson, S., Trunzo, M., Akhtar, L., Wynne, D. K., Lucas-Derse, S., Bolos, A. M., Tokola, R., Virkkunen, M., Linnoila, M., & Dean, M. (1994). D2 receptor genotype and linkage disequilibrium and function in Finnish, American Indian, and U. S. Caucasian patients. In E. S. Gershon & C. R. Cloninger (Eds.), *Genetic approaches to mental disorders* (pp. 327–344). Washington, DC: American Psychiatric Press.
- Heath, A. C., & Martin, N. G. (1993). Genetic models for the natural history of smoking: Evidence for a genetic influence on smoking persistence. *Addictive Behaviors*, *18*, 19–34.
- Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction*, *86*, 1119–1127.
- Henningfield, J. E., Schuh, L. M., & Jarvik, M. E. (1995). Pathophysiology of tobacco dependence. In F. E. Bloom & D. J. Kupfer (Eds.), *Psychopharmacology: The fourth generation of progress* (pp. 1715–1730). New York: Raven Press.
- Hurt, R. D., Sachs, D. P. L., Glover, E. D., Offord, K. P., Johnston, J. A., Dale, L. C., Khayrallah, M. A., Schroeder, D. R., Glover, P. N., Sullivan, C. R., Croghan, I. T., & Sullivan, P. M. (1997). A comparison of sustained-release bupropion and placebo for smoking cessation. *New England Journal of Medicine*, *337*, 1195–1202.
- Lerman, C., Caporaso, N., Main, D., Audrain, J., Boyd, N. R., Bowman, E. D., & Shields, P. G. (1998). Depression and self-medication with nicotine: The modifying influence of the dopamine D4 receptor gene. *Health Psychology*, *17*, 56–62.
- Lerman, C., Gold, K., Audrain, J., Lin, T. H., Boyd, N. R., Orleans, C. T., Wilfond, B., Louben, G., & Caporaso, N. (1997). Incorporating biomarkers of exposure and genetic susceptibility into smoking cessation treatment: Effects on smoking-related cognitions, emotions, and behavior change. *Health Psychology*, *16*, 87–99.
- Lerman, C., Shields, P. G., Main, D., Audrain, J., Roth, J., Boyd, N. R., & Caporaso, N. E. (1997). Lack of association of tyrosine

- hydroxylase genetic polymorphism with cigarette smoking. *Pharmacogenetics*, 7, 521-524.
- Newhouse, P. A., & Hughes, J. R. (1991). The role of nicotine and nicotinic mechanisms in neuropsychiatric disease. *British Journal of Addiction*, 86, 521-526.
- Noble, E. P., Blum, K., Ritchie, T., Montgomery, A., & Sheridan, P. J. (1991). Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Archives of General Psychiatry*, 48, 648-654.
- Noble, E. P., Noble, R. E., Ritchie, T., Sydulko, K., Bohlman, M. C., Noble, L. A., Zhang, Y., Sparkes, R. S., & Grandy, D. K. (1994). D2 dopamine receptor gene and obesity. *International Journal of Eating Disorders*, 15, 205-217.
- O'Neill, M. F., Dourish, C. T., & Iversen, S. D. (1991). Evidence for an involvement of D1 and D2 dopamine receptors in mediating nicotine-induced hyperactivity in rats. *Psychopharmacology*, 104, 343-350.
- Plomin, R. (1998). Using DNA in health psychology. *Health Psychology*, 17, 53-55.
- Plomin, R., Owen, M. J., & McGuffin, P. (1994). The genetic basis of complex human behaviors. *Science*, 264, 1733-1739.
- Pontieri, F. E., Tanda, G., Orzi, F., & Di Chiara, G. (1996). Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature*, 382, 255-257.
- Risch, N. (1990). Genetic linkage and complex diseases, with special reference to psychiatric disorders. *Genetic Epidemiology*, 7, 3-16.
- Sabol, S. Z., Nelson, M. L., Fisher, C., Gunzerath, L., Brody, C. L., Hu, S., Sirota, L. A., Marcus, S. E., Greenberg, B. D., Lucas, F.-R. IV, Benjamin, J., Murphy, D. L., & Hamer, D. H. (1999). A genetic association for cigarette smoking behavior. *Health Psychology*, 18, 7-13.
- Seeman, P., & Niznik, H. B. (1990). Dopamine receptors and transporters in Parkinson's disease and schizophrenia. *FASEB Journal*, 4, 2737-2744.
- Vandenberg, D. J., Persico, A. M., Hawkins, A. L., Griffin, C. A., Li, X., Jabs, E. W., & Uhl, G. R. (1992). Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. *Genomics*, 14, 1104-1106.
- Wise, R. A., & Rompre, P. P. (1989). Brain dopamine and reward. *Annual Review of Psychology*, 40, 191-225.

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