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Genetic Analysis of Polymorphisms in Dopamine Receptor and Transporter Genes for Association with Smoking among Cancer Patients

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Abstract

Background—Smoking among Russian cancer patients may be related to variation in *DRD2/ANKK1* (Taq1), *DRD4* (exon III VNTR), and *SLC6A3* genes.

Methods—750 patients provided smoking history and DNA.

Results—Current smokers were more likely to be *DRD2* A2 allele carriers, vs. non-smokers (former/never smokers; 69% vs. 56%; OR=1.69; 95% CI: 1.13–2.53, p=0.01) and former smokers (69% vs. 59%; OR=1.54; 95% CI: 0.97–2.46, p=0.07). Ever smokers (current/former smokers) were more likely to be *DRD2* A2 allele carriers, vs. never smokers (65% vs. 55%; OR=1.50; 95% CI: 1.00–2.27, p=0.05). Risk of current smoking among *DRD2* A2 allele carriers was present if the *DRD4* short allele was also present (OR=1.76; 95% CI: 1.12–2.78, p=.02) and the risk for ever smoking among *DRD2* A2 allele carriers was present if the *DRD4* short allele was also present (OR=1.62; 95% CI: 1.02–2.55, p=.04). *DRD2* A2 allele carriers had a shorter period of previous abstinence, vs. *DRD2* A1 carriers (p=.02). Effects were not statistically significant when controlling for multiple comparisons.

Conclusions—The *DRD2* A2 allele may increase risk of smoking among cancer patients, convergent with studies using non-Western samples. However, additional replication is needed.

Keywords

Tobacco; Russia; Cancer Patients; Gene; DRD2; DRD4; SLC6A3

Introduction

Continued smoking among cancer patients remains an ongoing public health problem, particularly in developing countries such as Russia. Upwards of about one-third of Russian cancer patients continue to smoke following diagnosis and intention to quit is relatively low [1–2]. Given the risks of continued smoking in this population, including diminished treatment efficacy, increased risk of death, and worsening of quality of life [3], identifying

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correlates of smoking among cancer patients for guiding treatment implementation is a priority.

Research on the neurobiology of nicotine dependence underscores the role of dopamine [4]. Nicotine binds to and stimulates nicotinic acetylcholine receptors (nAChRs) [5–6], increasing dopamine levels [7–8]. As with other drugs of abuse, this dopamine increase is experienced as rewarding and perpetuates drug dependence [9]. Polymorphisms in genes that modulate the effects of nicotine on nAChRs, therefore, have been examined as risk factors for nicotine dependence [10] and biomarkers of treatment response [11].

Variants of dopaminergic genes have been evaluated as correlates of smoking behavior. The Taq1A polymorphism situated on the *ANKK1* gene, located 10kb downstream in the 3′-flanking region of the dopamine receptor 2 gene (*DRD2*), decreases D2 receptor binding [12]. Initial studies linked the A1 allele to greater risk for smoking [13], nicotine dependence [14], and progression from experimenting with tobacco to regular use [15], however this relationship has not been consistently replicated [16]. The dopamine transporter gene, *SLC6A3*, which transports extra-cellular dopamine out of the synapse, has a 40bp functional repeat polymorphism, and the 9-repeat allele lowers transporter expression [17]. The *SLC6A3* 9-repeat polymorphism has been related to longer quit durations and a greater likelihood of cessation [18–20], although not in all studies [21]. Lastly, the functionality of *DRD4* exon III variable number tandem repeat (VNTR) polymorphisms has been identified, with the 'long' alleles (≥7 repeats) related to a blunted intracellular response to dopamine *in vitro*, vs. 'short' alleles (≤ 6 repeats) [22]. Individuals with long alleles are less likely to quit smoking [23–24] and report higher rates of smoking and a younger age of smoking initiation [14, 25]. However, this relationship was not replicated in a recent study [26].

To date, no study has examined these variants in association with smoking among cancer patients. Such a study should be large and include a sample with low ethnic admixture [27–28]. The present study evaluated the relationship between variants in genes functionally associated with dopamine availability with smoking in a large sample of Russian cancer patients. Results from this study may help guide treatments for a sub-group of smokers who are under-studied and at particular risk for adverse health consequences from smoking.

Methods

Patients

The study sample was comprised of 750 patients diagnosed with cancer within 30 days of study enrollment and receiving care at Tatarstan Regional Clinical Cancer Center (TRCC) in Kazan, Russia (Table 1). Participants were diagnosed with head and neck, colorectal, or lung cancer and were over age 18. These tumor sites were selected since they have a high frequency of smoking [1]. Eighty-nine patients refused to enroll or provided incomplete data (participation rate = 89%).

Procedures

All procedures were approved by the ethics committee at the TRCC. A designated Research Assistant (RA) used daily physician schedules to identify patients and determine eligibility and willingness to enroll in the study. Informed consent was ascertained. The RA conducted an assessment in a private clinic area, which included surveys and the collection of a blood sample for genetic analysis. Participants were given US$3.00 for completing the assessment. Smokers were given a smoking cessation treatment manual [29].

Measures

Demographic and Medical Data—Demographic information (e.g., gender, age) and medical data (e.g., tumor site) were collected.

Depression—The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item Likert measure used to assess depressive symptoms [30]. The CES-D was administered to control for variation in smoking behavior attributable to depression symptoms [2].

Genotyping—Blood samples were collected on FTA bloodspot cards and analyzed at the TRCC using polymerase chain reaction (PCR) methods. Genotyping of the *DRD2* TaqIA was performed using a fluorogenic 5′-nuclease assay as described in the NCI SNP500 Cancer Database (http://variantgps.nci.nih.gov/cgfseq/pages/home.do). A 25 ul TaqMan reaction was setup in a 96-well plate using 20ng of genomic DNA, 2XTaqMan Universal PCR MasterMix, 900 nM primers (Forward-5′-GTGTGCAGCTCACTCCATCCT Reverse-5′-GCAACACAGCCATCCTCAAA), and 200nM TaqMan-MGB probes (T Probe=FAM 5′-TGCCTTGACCAGCAC, C Probe=VIC 5′-TGCCTCGACCAGCA). Patients were identified as A1 (A1/A1 or A1/A2) or A2 (A2/A2) allele carriers. Genotyping of *SLC6A3* was performed according to past studies [31]. Genomic DNA was amplified for 35 cycles; each cycle consisted of denaturation for 1 minute at 93°C and annealing/elongation for 1 minute at 72°C. The following oligonucleotide primers were used: 5′-TGTGGTGTAGGGAACGGCCTGAG-3′ and 5′-CTTCCTGGAGGTCACGGCTCAAGG-3′. PCR products were electrophoretically separated on a 5% polyacrylamide gel and their molecular weights calculated by comparing their rate of migration with that of known molecular weight standards. The number of copies of the 40-base pair repeat present was determined from the size of the product. Participants were categorized as having the 9-repeat allele (i.e., 9/9 or 9/* vs. */* where * is alleles other than 9). Lastly, the 48 bp variable nucleotide tandem repeat of *DRD4* was assessed following procedures used previously [24]. The polymorphic region within exon 3 was amplified by PCR and fragments ranging from 270–570bp, containing 2–8 repeats, were resolved by electrophoresis on a 3% agarose gel and detected with ethidium bromide staining. Patients were coded as short (≤ 6 repeats) or long (≥ 7 repeats) allele carriers.

Smoking Behaviors—Our primary outcome was smoking status based on self-report and defined as current (i.e., smokes regularly, or cut down, or once in a while), former (i.e., used to smoke, but no longer does), or never (i.e., never smoked even a puff of one cigarette) smoker as done previously [1] and recommended with cancer patients [32]. As secondary outcomes, assessed only among current smokers, we examined age of initiation, years smoked, number of previous 24-hour quit attempts, longest duration of previous quit attempt, current smoking rate, and level of nicotine dependence measured by the Fagerström Test for Nicotine Dependence (FTND) [33].

Statistical Analyses

Descriptive statistics were computed to delineate the characteristics of the present sample. The chi-square likelihood ratio test was used to assess Hardy-Weinberg equilibrium. Separate multiple logistic regression models were examined for each gene and gene x gene interaction predicting smoking status. Following the methods of Das et al. [26], models compared current smokers to former smokers, current smokers to non-smokers (former and never smokers combined), and ever smokers (current and former smokers combined) to never smokers. Models controlled for gender, tumor type, and depression since these variables have been associated previously with smoking behavior among cancer patients [1,2]. Odds ratios and 95% confidence intervals were computed for predictors. By convention, the probability value of .05 or less was considered statistically significant but, to

be more conservative, a Bonferroni correction was applied for multiple comparisons as well. As done in a previous study [34], the correction was applied to each set of comparisons for the primary outcome (e.g., current vs. former smokers for the three main effects of each gene and the three interaction effects) and the secondary outcome (e.g., six dependent variables across *DRD2*). Thus, for each comparison, the adjusted p-value for significance testing was .009. Analysis of variance was used to assess differences between genetic alleles in terms of age of smoking initiation, years smoked, number of previous 24-hour quit attempts, longest duration of previous quit attempt, current smoking rate, and level of nicotine dependence. Power estimates calculated during the planning of this study assumed effect sizes for genetic associations based on previous studies in the general population [19,24,27]. Analyses were conducted using the Statistical Package for the Social Sciences (Version 20).

Results

Genetic Associations with Smoking Status

The frequencies of alleles for each gene are shown in Table 2. The present frequencies did not differ from the expected frequencies based on Hardy-Weinberg test of equilibrium (for *DRD2*, $\chi^2[1] = 1.95$, p = .16; for *DRD4*, $\chi^2[1] = 1.75$, p = .19; and for *SLC6A3*, $\chi^2[1] = 1.41$, p = .23). *DRD2* genotype was related to smoking status in two models based on the conventional p-value cut-off. Current smokers were more likely to be *DRD2* A2 allele carriers (A2/A2), vs. non-smokers (former and never smokers; 69% vs. 56%; OR = 1.69; 95% CI: 1.13–2.53, p = 0.01). Ever smokers (current and former smokers) were more likely to be *DRD2* A2 allele carriers (A2/A2), vs. never smokers (65% vs. 55%; OR = 1.50; 95% CI: 1.00–2.27, p = 0.05). In addition, current smokers were more likely to be *DRD2* A2 allele carriers (A2/A2), vs. former smokers, although this comparison represented only a trend based on convention (69% vs. 59%; OR = 1.54; 95% CI: 0.97–2.46, p = 0.07). Models for *DRD4* and *SLC6A3* yielded no significant relationships between genotypes and smoking status. Further, no model reached statistical significance based on the Bonferroni correction for multiple testing.

Two models that tested gene-gene interactions yielded significant relationships with smoking status based on the conventional p-value cut-off. Participants were more likely to be current smokers, vs. non-smokers (former and never), if they possessed the *DRD2* A2 allele (A2/A2) and the short allele for *DRD4* (72% vs. 55%), but not the *DRD4* long allele (62% vs. 58%; OR = 1.76, 95% CI: 1.12–2.78, p = 0.02). In addition, participants were more likely to be ever smokers (current and former), vs. never smokers, if they possessed the *DRD2* A2 allele (A2/A2) and the short allele for *DRD4* (67% vs. 54%), but not the *DRD4* long allele (60% vs. 57%; OR = 1.62; 95% CI: 1.02–2.55, p = 0.04). Further, no model reached statistical significance based on the Bonferroni correction for multiple testing.

Genetic Associations with Smoking Characteristics among Current Smokers

No associations were found between *DRD2*, *DRD4*, and *SLC6A3* alleles and age of initiation, years smoked, number of previous 24-hour quit attempts, current smoking rate, and level of nicotine dependence. Participants who were *DRD2* A2 allele carriers reported a significantly shorter previous quit attempt (M = 56.8 days; SD = 160.1), vs. carriers of the *DRD2* A1 allele (M = 152.9 days; SD = 411.7; F[1,190] = 5.44, p = 0.02), although this was not statistically significant based on the Bonferroni correction.

Discussion

The results of the present study suggest that risk of smoking may be associated with the A2 allele of *DRD2*. Using the conventional p-value cut-off, the A2 allele was related to a greater likelihood of continued tobacco use following diagnosis as well as ever being a smoker. In addition, *DRD2* A2 allele carriers reported a shorter average duration of past smoking cessation. As such, this patient sub-group may require targeted smoking cessation interventions, particularly if the short allele for *DRD4* is also present. However, when correcting for multiple comparisons, these relationships were no longer considered statistically significant. Such a correction may also increase the probability of a type II error. Thus, we discuss the present findings in relation to past studies, yet with a caution given the results when considering the correction for multiple testing.

The present results are divergent from studies that have identified the A1 allele for *DRD2* as a correlate of smoking [13,35]. However, studies using non-Western samples have found that the A2 allele for *DRD2* was associated with smoking. Two studies reported that the *DRD2* A2 allele was associated with greater risk of tobacco use in Japanese samples [36,37] as did a study with a Polish sample [34]. Taken together, these results are suggestive of the possibility that ethnic differences may influence the relationship between *DRD2* alleles and smoking. It is possible that other functional genetic variants, which differ across these ethnic groups, influence the relationship between *DRD2* alleles and smoking. Alternatively, cultural differences that covary with geographic and ethnic factors could moderate the relationship between *DRD2* alleles and smoking and explain these divergent findings across samples. It is also worth noting that a recent meta-analysis showed that the effects of *DRD2* genetic alleles vary across different smoking phenotypes (e.g., smoking persistence vs. smoking rate) and depend on the proportion of men in a particular sample [38]. The gender effect noted in this meta-analysis is particularly relevant given that the present sample was comprised of 65% males. Further, since the *DRD2* A1 allele is in linkage disequilibrium (LD) with other *DRD2* variants and possibly other variants of the *ANKK1* gene, it is plausible that other functional variants in *DRD2* influence smoking phenotypes. While it is unclear if the LD patterns for *DRD2* are different across the geographic regions, a previous study found variation in the relationship between *DRD2* variants and Parkinson's disease across racial/ethnic groups that may be attributable to differences in LD. [39]

The interaction with *DRD4*, suggesting greater risk for smoking among the short allele carriers, is inconsistent with previous studies as well [14,23,36]. However, among depressed smokers, carriers of the *DRD4* short allele are more likely to smoke to alleviate depression symptoms, an effect not detected among *DRD4* long allele carriers [40]. The high rate of depression in the present sample (64%, based on a cut-off of ≥ 16 on the CES-D) may explain the present finding, indicating that the relationship between *DRD4* alleles and smoking, in part, depends on the presence of depression symptoms [40].

The present results also suggest that variants of *DRD4* and *SLC6A3* may have little association with smoking phenotypes. While null findings concerning smoking phenotypes and these genes have been reported [21,26], it may also be the case that differences across studies in the definitions of smoking phenotypes explain contradictory findings. There was some indication in the present analyses that *DRD4* variants interact with *DRD2* variants to predict smoking phenotypes, so other gene x gene interactions not tested here may be important for other smoking phenotypes for *DRD4* and for *SLC6A3* variants.

Study limitations should be considered. First, although the present sample was relatively large, it may still have been inadequate to provide sufficient statistical power to consider gene x gene interactions. Second, when considering the results in terms of the correction for

multiple testing, there were no comparisons that reached statistical significance. As such, replication is critical to verify that the possible relationships noted in the present study were not found simply by chance. Third, while the rate of misreporting of smoking status is low in this population and unrelated to prediction models [1], the lack of bioverification of self-reported smoking may have affected study results. Fourth, the present study focused on only a certain subset of candidate genes and very recent data suggests a possible role of variants of genes not tested here such as variation in the neuropeptide Y gene promoter [41]. Fifth, the candidate gene approach assumes a narrow conceptual framework for understanding nicotine dependence. Recent methods in genetic analysis, including genome-wide and deep sequencing analysis, offer more powerful approaches to identifying genetic contributions to disease risk. Finally, the prevalence of never smoking in the present study (52%) was higher than found in previous studies (37–43%) [1–2], which may have affected the present results.

Nevertheless, the present findings contribute to the growing literature suggesting that the relationship between *DRD2* genetic variants and smoking may differ across Western and non-Western samples. Further, the present findings offer some support for the identification of *DRD2* A2 allele carriers and targeted treatment with smoking cessation treatments including bupropion. Previous studies have suggested that carriers of the *DRD2* A2 allele are more likely to respond to bupropion, compared to A1 allele carriers [42]. Given the high rate of tobacco use following diagnosis identified in these patients in the present study and in past studies [1,2], the need for empirical methods for targeted treatments for nicotine dependence is critical and hopefully will yield improved clinical outcomes for this under-studied population.

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Table 1

Descriptive Sample Data (N = 750)

Variable	N (%) or Mean (SD)
Sex[a]	
Male	492 (65.6%)
Female	257 (34.4%)
Marital Status[a]	
Married	539 (72.3%)
Single	10 (1.3%)
Separated/Divorced	46 (6.2%)
Widowed	151 (20.2%)
Age[a]	
Mean (SD)	62.6 years (10.9 years)
Education[a]	
Less Than Grade 8	68 (9.1%)
Grade 8–11	146 (19.5%)
High School Diploma	155 (20.7%)
Vocational School	229 (30.6%)
Some College	130 (17.4%)
College Degree	1 (0.1%)
Graduate Degree and Higher	19 (2.5%)
Income (US Dollars)[a]	
Mean (SD)	$4,159.8 ($2,536.2)
Cancer Type	
Head and Neck	107(14.3%)
Lung	184 (24.5%)
Colorectal	459 (61.2%)
Smoking Status	
Current	204 (27.2%)
Former	160 (21.3%)
Never	386 (51.5%)
Fagerström Test of Nicotine Addiction[b]	
Very Low	33 (16.7%)
Low	69 (34.8%)
Medium	42 (21.2%)
High	41 (20.7%)
Very High	13 (6.6%)
Number of Years Smoking	
Mean (SD)	39.2 years (12.0 years)
Average Number of Cigarettes in Past 30 Days[b]	
Mean (SD)	18.1 cigarettes (16.7 cigarettes)

Variable	N (%) or Mean (SD)
Age Started Smoking[b]	
Mean (SD)	18.6 years (7.8 years)
Number of Times Quit for at least 24 Hours[b]	
Mean (SD)	3.4 times (4.5 times)
Longest Duration of Previous Quit Attempt[b]	
Mean (SD)	87.5 days (265.7 days)
Depression (CES-D score ≥ 16)	
Depressed	532 (64.2%)
Not depressed	219 (26.4%)

Note.

[a] Indicates the presence of missing data;

[b] Includes current smokers only.

Table 2

Frequencies of Genetic Alleles by Smoking Status

Gene	Current Smokers N (%)	Former Smokers N (%)	Never Smokers N (%)	Non-Smokers[a] N (%)	Ever Smokers[b] N (%)
DRD2					
A1/A1 or A1/A2	62 (31%)	65 (41%)	172 (45%)	237 (44%)	127 (35%)
A2/A2	140 (69%)[1, 3]	92 (59%)[1]	209 (55%)[2]	301 (56%)[3]	232 (65%)[2]
DRD4					
Short (≥ 6 repeats)	146 (73%)	108 (70%)	279 (73%)	387 (73%)	254 (72%)
Long (≥ 7 repeats)	55 (27%)	46 (30%)	101 (27%)	147 (27%)	101 (29%)
SLC6A3					
9-repeat allele	62 (30%)	52 (33%)	96 (25%)	148 (27%)	114 (31%)
10-repeat allele	142 (70%)	108 (67%)	290 (75%)	398 (73%)	250 (69%)

Note.

[a] former and never combined;

[b] current and former combined;

[1] comparison with matching superscript indicates p = .07;

[2] comparison with matching superscript indicates p = .05;

[3] comparison with matching superscript indicates p = .01.

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