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Waterpipe Smoking And The DRD2/ANKK1 Genotype

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Abstract

Background—Waterpipe smoking is increasingly a worldwide phenomenpn. Few studies have been conducted on the epidemiology of waterpipe smoking behavior and its genetic determinants. A polymorphism (TaqI) in the 3′ untranslated region of the dopamine receptor gene (DRD2), later localized to the neighboring ANKK1 gene, has been previously linked to cigarette smoking. Since all tobacco products' share the ability of stimulating the dopaminergic reward system, variation in the DRD2 genotype might be associated with waterpipe smoking addiction.

Aim—This study aims to explore genetic variations in DRD2 gene and waterpipe smoking, motives and addiction in Egyptian rural males.

Material and Methods—The subjects (N=154) were selected from participants in a household smoking prevalence survey if they were adults, males, currently smoking waterpipe and not smoking cigarettes. Participants were interviewed about their smoking behaviors. Blood samples were genotyped by polymerase chain reaction (PCR). Subjects were subsequently classified as either the A1 (presence of at least one A1 allele) or A2 group (A2 homozygotes).

Results—The prevalence of Al genotype was 34.4 % in current waterpipe users, and was associated with the maximum duration before smokers experienced craving to smoke: after adjusting for age of smoking initiation, smoking for addictive motives, and average daily tobacco consumption, the A1 carriers were more likely to experience craving within a shorter duration after abstinence (the first 24 hours) compared to subjects with A2/A2 genotype (Odds ratio [OR] 2.70, 95% confidence interval [CI]: 1.18 – 6.23). In addition, the frequent visitors of shisha cafes were more likely to be younger, heavy smokers and carriers of A1 allele (OR, 2.52, 95% CI: 1.06-6.02).

Conclusion and Recommendations—This study revealed that the maximum duration before experiencing craving to smoke waterpipe and frequency of visiting cafes to smoke may be influenced by an inherited variations in the DRD2 genotype.

Keywords

DRD2 gene; genetic; smoking; tobacco addiction; waterpipe

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Introduction

Waterpipe smoking (also known as Shisha, Hookah, Hubble Bubble) is increasingly a worldwide phenomenon, with an estimated 100 million daily users.[1] It has been used for many centuries under the illusion that it is a safe way to smoke tobacco.[2] Waterpipe smoking is widely spread in many Middle Eastern countries particularly among youth of both sexes. The recent revival in waterpipe use has been demonstrated in national and local surveys in Egypt,[3] Kuwait, [4] and Lebanon.[5]

Dependence on tobacco has been primarily attributed to the ability of nicotine to stimulate the reward circuit in the brain, which is similar to the biological mechanism of dependency for abuse of other substances. [6,7] The possibility of genetic influences on tlus mechanism has been considered in the context of candidate genes in the dopaminergic reward system pathway.[6] The D2 dopamine receptor gene is located on chromosome 11 (q22-23) and has multiple allelic forms.[7] Blum et al., (1990)[8] described a restriction fragment length polymorphism (RFLP)(TaqI) in the 3′ untranslated region, later localized to the neighboring ANKK1 gene[9] with alleles designated as DRD2*A1 and *A2. The A1 allele has been associated with a reduced number of dopamine binding sites in the brain, and is hypothesized to influence addiction by causing a hypodopaminergic state that is alleviated by chronic exposure to nicotine[8]

Research on the genetics of smoking has increased our understanding of nicotine dependence, and it is likely to illuminate the mechanisms by which smoking adversely affects the health of smokers.[10] An improved overall understanding of addiction, coupled with identification of genetic markers predictive of nicotine dependence, has been instrumental in the development of medications and behavioral treatments for nicotine addiction burden. It may also help in improving cessation rates, achieved by using genotyping to match smokers to appropriate cessation interventions.[10,11]

The evidence that waterpipe use involves self administration of the psychoactive substance “nicotine” is supported by the results of several studies wluch have shown that there are substantial amounts of nicotine in both flavored and unflavored waterpipe tobacco,[12] in the smoke produced by waterpipe,[13] and in the plasma of waterpipe smokers.[14] The results from these studies suggest that relative to cigarette use, waterpipe use can deliver the same or greater doses of nicotine.[15] Furthermore, Maziak et al., (2005)[16] in their study pointed out that waterpipe smokers manifested some features of tobacco dependence such as increased use over time, decreased belief in one's ability to quit, continued use despite a desire to quit, and the perception that one is “hooked” on waterpipe.

It has been hypothesized that subjects with A1 alleles exhibit a deficiency in the dopaminergic system, whereby they compensate by using nicotine or other addictive substances to enhance doparnine release in the brain.[6, 8, 17] Our study aimed to assess associations between the DRD2/ANKK1 genotypes and smoking behaviors in a population of habitual waterpipe users who used it as their sole means of tobacco smoking.

Materials and Methods

Study participants and procedures

Participants were recruited from a baseline conununity-based survey of 9 villages in the Qalyubia Governorate in the Nile delta region of Egypt in 2003-2004, where a household smoking prevalence survey was carried out. In each village, 300 households were selected using a systematic random sampling method; 10,160 adults of 11,300 who were contacted (>90% participation rate) were interviewed for molecular epidemiology studies.[18] The

survey estimated that about 11% of adult males and < 1% of adult females had ever smoked any tobacco product, and 6% of adult males were currently smoking waterpipe exclusively. Participants for the current study were adult males (18 yrs and above) who currently smoke waterpipe, specifically those who smoked at least once per week in the past 4 weeks.[19] Exclusion criteria were inability to give an informed consent and being a current cigarette smoker. All eligible individuals were invited to undergo a second, more extensive interview focused on waterpipe tobacco use. Out of the 160 potential subjects from the baseline survey who met these criteria, 154 (96%) agreed to participate in the second survey and provided informed consent. The study protocol and human subject's protection procedures were approved by the Institutional Review Boards of the Ministry of Health and Population in Egypt, and of University of Maryland Baltimore, USA.

Measures

Data were obtained using a 52-item questionnaire designed for the present study and covering five general domains: demographics, smoking behavior, nicotine dependence, craving and smoking motives.

The demographics section included age, marital status, educational attainment, and occupation. Smoking behavior variables included age of initiation of waterpipe smoking, average number of tobacco units (hagars) smoked per day, average number of hagars smoked in the past week, the duration of smoking waterpipe, attempt to quit smoking, frequency of visiting shisha cafes to smoke waterpipe and sharing the waterpipe with others. The pattern of inhalation of tobacco smoke was assessed using the question, “When you smoke do you usually inhale the smoke deep into your chest? ” (yes/no). Nicotine dependence was assessed using individual items of the modified version of the Fagerstrom test for nicotine dependence (FTND)[20] Craving for tobacco was assessed by asking the participants about the maximum time they could endure before experiencing a strong “desire” to smoke waterpipe (several hours, one day, several days but less than a week, or more than one week). Finally, to assess smoking motives, the subjects completed a modified version of the Horn–Waingrow Reasons for Smoking (RFS) Scale.[21] These subscales included, smoking to relieve negative affect, addictive smoking, smoking for stimulation and physiological and non physiological smoking. Each subscale is the sum of the individual items ranked on a Likert scale from 0 (not at all) to 3 (very much so). Annex 1 lists the questions that were asked using the modified FTND and RFS instruments (modified by substituting the word cigarette with shisha) to inquire about waterpipe-specific behaviors.

Genetic testing

Blood samples were collected and dried on a blood spot card for molecular analysis of the DRD2/ANKK1 A allele polymorphism using an established PCR-based assay following DNA extraction, and then RFLP enzymatic digestion and gel electrophoresis.[22] Genomic DNA was extracted from the blood spot cards (Schleicher & Schuell; Dassel-Germany) using the Gentra kit (Gentra DNA purification solution, Minneapolis, USA). Three DRD2 TaqI A genotypes were identified: (a) the homozygote A2A2, indicated by two fragments, 180 and 130 bp; (b) the heterozygote A1A2, revealed by three fragments, 310, 180, and 130 bp; and (c) the rare homozygote A1A1, shown by the uncleaved 310-bp fragment.

Statistical analysis

Descriptive analyses were conducted to examine frequencies of genotypes and the ranges and distributions for all continuous variables. The chi-square test (or Fisher exact test) and the Mann-Whitney U test were used to assess differences between genotypes and categorical and skewed continuous variables, respectively. The chi-square test was also used to assess whether the distribution of genotypes was in Hardy-Weinberg equilibrium. Given the low

frequency of the A1A1 genotype in this population, and for consistency with previous research, we compared subjects with any A1 allele (A1/A1 and A1/A2 combined) to those with the A2/A2 genotype.[22, 23] In univariate analysis the maximum time that smokers could abstain from smoking before experiencing craving to smoke a waterpipe and the frequency of visits to shisha cafes were significantly associated with DRD2 genotype. We constructed two logistic regression models for the relationship between these variables and DRD2 genotypes (dependent variable) adjusting for age, age of initiation of smoking, level of education, and average daily hagar consumption and smoking for addictive motives (the independent variables): the odds ratio (OR) and 95% confidence interval (CI) were used to estimate the strength of association and statistical significance, respectively. The SPSS software (release 12) was used for data analysis. All statistical tests were two sided with alpha=0.05.

Results

Study population

Overall, 154 current waterpipe users participated in the study with a response rate of 96%; the mean age was 47±14 years (range: 19-88). Almost all of these rural male participants were married (95%), and the majority had received no formal education (67%) and were working either in agriculture or in manual labor (76.5%). The mean age of initiation of waterpipe smoking was reported to be 22±9 years. The prevalence of daily waterpipe use was higher than 95% in the selected waterpipe users, with an average daily tobacco consumption of 4±8 hagars. Almost all these subjects owned their own waterpipe (98%).

Genotypes

Of the 154 participants, we successfully genotyped 151 for DRD2/ANKK1. The allele frequencies for A1 and A2 were 19% and 81% respectively and were in Hardy-Weinberg equilibrium ($x^2 = 1.23$, $P<0.27$). There were no significant differences in the distribution of A1 and A2 alleles by demographic characteristics Table (1).

Genotypes and smoking behavior and dependency

The results of the current study identified no significant association between the genotypes and smoking behaviors (Table 1). Generally, individuals who carried the A1 genotype reported on average a higher number of hagars consumed in the previous week (37 hagars vs. 32; p = 0.25), less tendency to quit smoking (53.8% vs. 67.7%; p = 0.09) and a shorter duration of the longest quit attempt (65.7 ±189 days for Al genotype vs. 82.3 ±271 days for A2 genotype; p = 0.27) Table (1).

However, a statistically significant association was observed between the genotype and the maximum duration before the subjects experienced cravings to smoke (Table 2). After adjusting for age of smoking initiation, smoking for addictive motives, and average daily tobacco consumption, the A1 carriers were more likely to experience craving within a shorter duration after abstinence (the first 24 hours) compared to subjects with A2/A2 genotype (OR 2.70, 95% CI: 1.18 – 6.23). In addition, A1 carriers were more likely to smoke >4 hagars per day (OR 2.50, 95% CI: 1.12-5.60), and were more likely to have a high addiction score (>3) on the RFS subscale (OR 3.94, 95% CI: 1.70-9.14) (Table 2). Furthermore, a higher proportion of the more frequent visitors to waterpipe cafes carried the A1 genotype when compared to less frequent visitors: specifically, frequent visitors to cafes were more likely to be younger in age, heavy smokers, and carriers of the A1 genotype (OR 2.52, 95% CI: 1.06-6.02) (Table 3).

Discussion

In the current study we examined genetic susceptibility to tobacco use and dependency in habitual waterpipe smokers in rural Upper Egypt. Results from previous research on cigarette smokers have provided evidence for the heritability of nicotine dependency[24] and for the identity of specific candidate genes in the doparninergic pathway[2527]. Accordingly, we genotyped the smokers in o w study for the DRD2/ANKK1 polymorphism, and found that the prevalence of the A1 allele was 34.4 %, comparable to the prevalence reported by studies on current cigarette smokers.[22, 28, 29] However, the results of the present study did not replicate the association between tobacco behavior and the DRD2 genotype previously described for cigarette smokers.[29]

Besides the complexity of smoking behavior, with multiple genetic and environmental factors contributing to its variance,[30] many factors appear to distort the results of genetic association studies,[31] including disparity in allele frequencies, population stratification, and lack of attention to psycho-social covariates.[6,31]

The DRD2 genotype was significantly associated in our study with the maximum duration before craving to smoke. Craving is a crucial motive for substance use that reflects negative reinforcement, and it has been suggested as a useful phenotype for research on genetic factors related to nicotine dependence,[32] Although the question we used in assessing craving was subjective, it correlated significantly with all the smoking behavior variables in our survey, and with quit attempts, FTND questions, and smoking motivation scales. Our results revealed that smokers with the A1 genotype exhibited shorter time to craving after abstinence. This notion lends support to recent research which reported a significantly stronger stress-induced and cue-induced cigarette craving in individuals carrying the A1 variant.[33] Personality traits such as sociability have been previously linked to risk taking behaviors including smoking, and were found to be influenced by genetic factors.[22, 34] The most consistently reported association between smoking behavior and personality relates to the personality dimensions of sensation seeking and extraversion.[35]

Many of these personality traits are heritable, and there is increasing support for the notion that the genetic influence on smoking initiation is mediated by personality[36] In the present study, despite the fact that almost all smokers owned a waterpipe, one third of them visited the cafes to smoke. This suggests the possibility that frequent visitors to the cafes do so because of socially-driven motives for smoking. Such subjects had higher tobacco consumption than non-visitors, and exhibited features of physical dependence on tobacco, as assessed by analysis of the FTND. These findings are consistent with studies that have related extraversion (a personality trait highly related to sociability) to cigarette smoking.[37,38] In addition, frequent visitors to waterpipe cafes were more likely to carry the A1 genotype, consistent with previous studies that linked this allele with personality traits.[28,39,40]

Conclusion and Recommendations

This study revealed that both the maximum duration before experiencing cravings to smoke a waterpiye and the frequency of visiting shisha cafes may be influenced by inherited variations in the DRD2/ANKK1 genotype. However, the study has the following limitations: The assessment of dependence and smoking motives in waterpipe smokers was hampered by the lack of validated tools specifically designed for this mode of tobacco smoking, and we had to modify existing instruments such as the FTND and RFS scales for this study. There was a lack of information on the nicotine content of the hagars, which may have jeopardized the accurate characterization of tobacco consumption. Finally, our focus on a single gene while examining a polygenic trait such as smoking might be problematic. Future studies are

needed for the development of standardized and validated methods for characterizing waterpipe smoking behavior, for use in expanded research on the multiple genetic and psychosocial predictors of this behavior.

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Appendix

Annex (1)

Modified Versions Of The FTND And RFS Scales for Waterpipe Smokers

Reasons for. smoking:	***Not at all 0***	***A little I***	***Quit a hit 2***	***Very much so 3***
I light up shisha when I'm uncomfortable or upset				
Smoking shislia helps me to think and concentrate				
I get a real gnawing hunger to smoke when I have not smoked for a while				
When I feel blue or want to take my mind off cares and worries, I smoke shisha				
1 smoke more when I'm rushed and have lots to do				
I find it unbearable when 1 run out of shisha				
I smoke shisha when I feel angry				
Smoking shisha helps me keep going when I am tired				
Without a sliisha I do not know what to do with hand				
1 get a definite lift and feel more alert when smoking				

Modified version of the FTND	**Responses**
Numbers of hagars smoked daily	….hagars
How long after you wake up you feel you need to smoke shisha'?	….hours
Which one shisha you hate to give up during the day'?	Morning shisha ….1 Other one……0
Do you smoke more frequently in the morning than in the rest of the day?	No ……0 Yes……1
Do you smoke even when ill and bed ridden?	No ……0 Yes……1

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Table (1)

Association between Genotype DRD2, Demographics, Smoking Behavior Variables, Measures of Tobacco Dependence and Smoking Motives Genotype, P-Value

Characteristics	Genotype				p-value [a]
	A1/A1 A1/A2 n=52		A2/A2 n=99		
Demographics:					
Age (years)					
Mean (SD)	46	(13.6)	47.7	(14.2)	0.33
Marital status (139) *n*(%)					
Single	3	(6.0%)	4	(4.5%)	0.70 +
Ever married	47	(94.0%)	85	(95.5%)	
Education (140) **n** (%)					
No formal education	29	(58.0%)	65	(72.2%)	0.08
Formal **education**	21	(42.0%)	25	(27.8%)	
Smoking Behavior:					
Age of smoking initiation	21	(6.6)	22.8	(10.2)	0.46
Mean (SD)					
Number of hagars smoked / **day**	6.6	(7.2)	6.6	(8.3)	0.74
Mean (SD)					
Number of hagars **smoked in the past week**	37.6	(27.4)	32.5	(27.3)	0.25
Mean (SD)					
Inhalation of tobacco smoke (151): *n*(%)					
No	41	(78.8%)	82	(82.8%)	0.55
Yes	11	(21.2%)	17	(17.2%)	
Quit attempt (151) *n*(%)					
No	24	(46.2%)	32	(32.3%)	0.09
Yes	28	(53.8%)	67	(67.7%)	
Duration of the maximum quit time (days)	65.7	(189.7)	82.3	(271.9)	0.27
Mean (SD)					
Time to first shisha (hrs)	2.9	(3.8)	3.1	(3.6)	0.26

Characteristics	Genotype				
	A1/A1 A1/A2 n=52		A2/A2 n=99		p-value [a]
Mean (SD)					
Morning smoking (151) *n*(%)					
No	45	(86.5%)	90	(90.9%)	0.40
Yes	7	(13.5%)	9	(9.1%)	
Smoking when ill (150) *n*(%)					
No	44	(84.6%)	85	(86.7%)	0.72
Yes	8	(15.4%)	13	(13.3%)	
Smoking dependence					
Maximum duration before craving (150) *n*(%)					
Less than a day	38	(74.5%)	57	(57.6%)	0.04*
A day or more	13	(25.5%)	42	(42.4%)	
Smoking to relieve -ve affect	5.4	(3.1)	5.4	(3.0)	0.97
Mean (SD)					
Addictive smoking	4.0	(2.7)	3.7	(3.0)	0.50
Mean (SD)					
Stimulation	4.4	(3.9)	4.1	(3.7)	0.70
Mean (SD)					
Physiological	7.5	(5.1)	6.9	(4.9)	0.50
Mean (SD)					
Non Physiological	6.3	(3.6)	6.2	(3.7)	0.99
Mean (SD)					
Frequency of visiting shisha cafe *(151) n* (%)					
No visits	31	(59.6%)	78	(78.8%)	0.01*
Once or more/week	21	(40.4%)	21	(21.2%)	
Sharing shisha *(151) n* (%)					
No	11	(21.2%)	29	(29.3%)	0.28
Yes	41	(78.8%)	70	(70.7%)	

[a] p value using chi-square comparisons for categorical variables or Mann-Whitney tests for continuous variables.

*=Significant at p ±0.05

+ p value of Fisher exact test

Table (2)

Factors Related to Duration before Experiencing Craving to Smoke Shisha According to Logistic Regression Analysis

Predictors	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
			Upper	Lower
DRD2 genotype (A1 vs. A2)	0.0 1	2.70	1.17	6.22
Average **hagars** /day (> 4 hagars/day vs. ≤4 hagars/day)	0.02	2.50	1.12	5.60
Age of initiation (> 20 years vs. ≤ 20 years)	0.31	1.51	0.67	3.38
Addictive smoking scores (>3 vs. ≤ 3)	0.00	3.94	1.70	9.14

Table (3)

Factors Related to Frequency of Visits to Shisha Cafes to Smoke Shisha According to Logistic Regression Analysis

Predictors	Sig.	EXP(B)	95.0% C.I. for EXP(B)	
			Upper	Lower
Age	0.00	0.93	0.89	0.97
DRD2 genotype (Al vs. A2)	0.03	2.52	1.06	6.02
Average **hagars/day** (> 4 hagars/day vs. ≤ 4 hagars/day)	0.03	2.58	1.06	6.27
Age of initiation (> 20 years vs. ≤ 20 years)	0.10	0.46	0.18	1.17
Education (Formal vs. non formal education)	0.69	1.20	0.47	3.05