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ORIGINAL PAPER

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Polymorphisms in the DBH and DRD2 gene regions and smoking behavior

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Abstract The DRD2 *Taq*I A and DBH-1021 C/T polymorphisms were genotyped in smoking alcoholics (N = 100), non-alcoholic smokers (N = 120) and non-smoking controls (N = 112). Alcoholic and non-alcoholic smokers presented a higher frequency of the DRD2 *Taq*I A1 allele (P = 0.04) than non-smoking controls. Individuals who had at least one DBH-1021 T allele smoked fewer cigarettes per day than CC homozygotes (P = 0.03). These results are coherent with the expected effects of these polymorphisms on dopaminergic function.

Key words dopamine · dependence · alcoholism · nicotine

Introduction

The *Taq*I A polymorphism of dopamine D2 receptor gene (DRD2) (dbSNP ID rs1800497) has been implicated in substance use disorders. While most studies focused on alcoholism (Noble 2003), recent meta-analyses showed a higher prevalence of the DRD2 *Taq*I A1 allele in smokers than in non-smokers (Li et al. 2004) and verified a significant effect of this polymorphism on smoking initiation (Munafò et al. 2004).

The DRD2 gene is located on chromosome 11q22–23 (Grandy et al. 1989) and the *Taq*I A polymorphism is localized 9.5kb downstream from the DRD2 gene (Grandy et al. 1993). Neville et al. (2004) and Dubertret et al. (2004) showed that the *Taq*I A is an amino-acid changing (p.Glu713Lys) SNP in a previously undescribed protein kinase gene (ankyrin repeat and kinase domain containing 1-ANKK1). There is no consensus on the functionality of this polymorphism. Dubertret et al. (2004) detected the ANKK1 expression in the brain. However, the Neville et al. 2004 findings did not support a role of this gene on addictive behavior, since they did not detect the expression in the brain, and considered the amino acid substitution as unlikely to affect structural integrity. On the other hand, the *Taq*I A1 allele has been associated with reduced D2 receptor availability in the striatum (Thompson et al. 1997; Noble et al. 1991), lower mean relative glucose metabolic rate in dopaminergic regions (Noble et al. 1997), and low receptor density (Jonsson et al. 1999; Pohjalainen et al. 1998). Although there is more evidence pointing towards a role of the *Taq*I A in DRD2 than in ANKK1, the precise mechanism remains unknown. More specifically, it remains to be elucidated if the associations involving the *Taq*I A polymorphism are due to its own functionality or due to linkage disequilibrium with another variation within DRD2 or within this kinase gene. Considering that the DRD2 *Taq*I A notation is well established in the literature, it continues to be used in the genetic association studies.

The dopamine beta-hydroxylase gene (DBH), located on chromosome 9q34 (Craig et al. 1988), is another candidate gene in the development of addictive behaviors. The gene sequence comprises 22.98 kb, with a transcript of 2760 bp coding for a 603 aa protein. Dopamine beta-hydroxylase (DβH) is the enzyme that converts dopamine to norepinephrine. Molecular markers at the DBH locus were shown to be associated with variation in plasma-DβH activity (Wei et al. 1997; Cubells et al. 1998, 2000) and with DβH cerebrospinal-fluid levels (Cubells et al. 1998). Zabetian et al. (2001) identified a functional polymorphism (–1021 C/T; NCBI dbSNP ID 1611115) that accounted for 35 %–52 % of the variation in plasma-DβH activity in samples from different populations. Alterations in the enzyme activity levels have been reported in several psychiatric disorders including conduct disorder (Rogeness et al. 1984, 1986, 1987, 1988;

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Galvin et al. 1991), schizophrenia (Wei et al. 1997, 1998), psychotic depression (Cubells et al. 2002) and alcoholism (Kohnke et al. 2002).

A series of studies were conducted on DBH influences in smoking. McKinney et al. (2000) studied the DBH-1368 G/A polymorphism, and found that smokers with the DBH-1368 GG genotype smoked fewer cigarettes than those with GA/AA. Nevertheless, in a follow-up study (Johnstone et al. 2002), this result was not confirmed. Afterwards, the short-term effectiveness of the nicotine patch was tested in smokers genotyped for DRD2 *Taq*I A and DBH-1368 polymorphisms (Johnstone et al. 2004). The greatest benefit from this replacement therapy was reported by carriers of the DRD2 *Taq*I A1 allele, particularly when combined with the DBH-1368 A variant. It is noteworthy that the DBH-1368 G/A and –1021 C/T polymorphisms are not in strong linkage disequilibrium (Zabetian et al. 2003).

The present study analyzes the possible associations between the DRD2 *Taq*I A and DBH-1021 C/T polymorphisms with smoking behavior in alcoholics and non-alcoholics. Although several studies were performed with DRD2 *Taq*I A RFLP, this is the first investigation on the functional DBH-1021 C/T polymorphism and smoking.

Subjects and methods

Subjects

The European-derived population from south Brazil, where this study was performed, is mainly of Portuguese descent, but Italians, Spaniards and Germans have also contributed to its genetic composition (Salzano and Freire-Maia 1970). The African contribution to the gene pool in Rio Grande do Sul is smaller than in other Brazilian states (IBGE 2002). African-derived individuals constitute no more than 14% of the population in this region (Salzano and Freire-Maia 1970). The ethnicity of the samples studied here was ascertained by skin color and morphological characteristics (Salzano and Bortolini 2002).

A clinical sample of European-derived smoking alcoholic men (n = 100) was obtained in an alcoholism treatment ward. The diagnosis of alcohol dependence followed the DSM-III-R criteria (American Psychiatric Association 1987), and the interviews were performed with the Semi-Structured Assessment for the Genetics in Alcoholism (Bucholz et al. 1994).

A sample of 232 European-derived men (120 non-alcoholic smokers and 112 non-smoking controls) was assessed in a blood bank. Exposure to alcohol was measured by the CAGE questionnaire (Ewing 1984) and by inquiring about the type, quantity and frequency of alcoholic beverage consumption. None of the individuals in this group was a likely alcohol dependent.

The criterion for smoking in the alcoholic and non-alcoholic samples was daily use for at least one month. All individuals sampled signed an informed consent approved by the Ethics Committee of the Federal University of Rio Grande do Sul.

Genotyping

The DNA was extracted by the salting out procedure described by Lahiri and Nurnberger (1991). The polymorphic regions in DRD2 and DBH were amplified using primers and PCR conditions described by Grandy et al. (1993) and Köhnke et al. (2002), respectively. *Taq*I digestion reveals a two-allele polymorphism with an undigested band of 310bp (A1 allele) and two bands of 180bp and 130bp (A2 allele). The *Hha*I digestion in the DBH promoter region identifies a two-allele polymorphism with an undigested band of 130bp (T allele) and two bands of 110bp and 20bp (C allele).

Statistical analysis

The analyses of Hardy-Weinberg equilibrium and comparisons among smoking alcoholics, non-alcoholic smokers and non-smoking controls were performed using the chi-square test.

Taking into consideration the small number of DRD2 *Taq*I A1A1 and DBH-1021 TT homozygous individuals, they were analyzed together with the heterozygous genotypes to increase statistical power.

In order to evaluate the influence of genotypes (presence of DRD2 *Taq*I A1 allele and presence of DBH-1021 T allele) controlling for the sample origin (alcoholic smokers or non-alcoholic smokers) on the daily number of cigarettes smoked, we performed a two-way ANOVA. The average daily number of cigarettes smoked was normalized by the square root transformation.

The DBH X DRD2 interactions on smoking risk and daily number of cigarettes smoked were tested by the interaction terms in logistic regression and two-way ANOVA, respectively.

Results

The genotype frequencies in both polymorphisms were in Hardy-Weinberg equilibrium (Table 1). DRD2 *Taq*I A1 allele frequency was smaller (P = 0.04) in the group of non-smoking controls (Table 1). The prevalence of the A1 allele (A1A1 + A1A2 vs. A2A2) in this group was smaller than in alcoholic smokers and non-alcoholic smokers (P = 0.02). On the other hand, DBH-1021 C/T genotype and allele frequencies did not differ significantly among the three groups. There was no significant interaction between DRD2 and DBH genotypes on smoking risk (Table 1).

Individuals with and without the *Taq*I A1 allele did not differ on the average daily number of cigarettes smoked (P = 0.47); however, individuals that have at least one DBH-1021 T allele smoked fewer cigarettes (P = 0.03) than CC homozygous. There was no significant DRD2 X DBH interaction on the number of cigarettes smoked (Table 2).

Discussion

The results presented here confirm previous reports of association between DRD2 and nicotine dependence and provide suggestive evidence that the DBH gene may influence smoking behavior.

The DRD2 result is in accordance with a number of studies and was confirmed in the meta-analyses of Li et al. (2004) and Munafò et al. (2004). A new finding in the present study is the gradient observed. The frequency of the A1 allele is very similar in the two groups of smokers (alcoholics and non-alcoholics). Combining both groups, the difference to the non-smoking controls is higher than the one observed in the three-groups analysis ($\chi^2 = 7.54$; d. f. = 1; P = 0.006). We reported previously an association between the *Taq*I A1 allele and

Table 1 Smoking habit, alcoholism and DRD2 and DBH genotypes and alleles

	DRD2								DBH							
	A1A1		A1A2		A2A2		A1	A2	TT		CT		CC		C	T
	n	%	n	%	n	%	%	%	n	%	n	%	n	%	%	%
Alcoholic smokers (n = 100)	5	5.0	45	45.0	50	50.0	27.5	72.5	8	8.0	43	43.0	49	49.0	70.5	29.5
Non-alcoholic smokers (n = 120)	6	5.0	47	39.2	67	55.8	24.6	75.4	11	9.2	34	28.3	75	62.5	76.7	23.3
Non-smoking controls (n = 112)	4	3.6	31	27.7	77	68.7	17.4	82.6	6	5.3	44	39.3	62	55.4	75.0	25.0

DRD2 Hardy-Weinberg equilibrium: alcoholic smokers: $\chi^2 = 1.65$, $P > 0.20$; non-alcoholic smokers: $\chi^2 = 0.38$, $P > 0.20$; non-smoking controls: $\chi^2 = 0.15$, $P > 0.20$
Comparison among alcoholic smokers, non-alcoholic smokers and non-smoking controls: Genotype frequency: $\chi^2 = 8.23$; d.f. = 4; $P = 0.08$
Allele frequency: $\chi^2 = 6.57$; d.f. = 2; $P = 0.04$
Presence of the A1 allele (A1A1 + A1A2 vs. A2A2): $\chi^2 = 8.17$; d.f. = 2; $P = 0.02$

DBH Hardy-Weinberg equilibrium: alcoholic smokers; $\chi^2 = 1.09$, $P > 0.20$; alcoholic smokers: $\chi^2 = 5.21$, $P > 0.20$; non-smoking controls: $\chi^2 = 0.40$, $P > 0.20$
Comparison among alcoholic smokers, non-alcoholic smokers and non-smoking controls: Genotype frequency: $\chi^2 = 6.54$; d.f. = 4; $P = 0.16$
Allele frequency: $\chi^2 = 2.27$; d.f. = 2; $P = 0.32$
Presence of the T allele (TT + CT vs. CC): $\chi^2 = 4.06$; d.f. = 2; $P = 0.13$

DRD2 X DBH interaction: $\chi^2 = 0.00$; $P = 0.96$

Table 2 Daily number of cigarettes smoked and DRD2 and DBH genotypes

	DRD2		DBH	
	A1A1 + A1A2	A2A2	TT + CT	CC
Alcoholics				
N (99)	50	49	50	49
Number of cigarettes/day (average)	22.2	24.3	21.1	25.4
SE	1.8	1.8	1.8	1.8
Non-alcoholics				
N (120)	53	67	45	75
Number of cigarettes/day (average)	18.1	18.2	16.6	19.1
SE	1.8	1.6	1.9	1.5

Two-way ANOVA results:

DRD2 Alcoholics vs. non-alcoholics: $F = 11.69$, $P = 0.0007$; A1A1 + A1A2 vs. A2A2: $F = 0.51$, $P = 0.47$

DBH Alcoholics vs. non-alcoholics: $F = 13.31$, $P = 0.0003$; TT + TC vs. CC: $F = 4.57$, $P = 0.03$

DRD2 X DBH interaction: $F = 0.27$; $P = 0.60$

alcoholism (Bau et al. 2000). Taking into consideration the fact that most alcoholics in ours and other previous reports were smokers, future studies on DRD2 and alcoholism should be controlled for smoking, prompting the need for samples of non-smoking alcoholics. Since there is a common heritability between alcoholism and smoking (True et al. 1999), it is not unexpected if the *Taq*I A1 allele influences both disorders.

According to the model proposed by Cubells and Zabetian (2004), the DBH-1021 T allele can lead to a less efficient conversion of dopamine to norepinephrine, increasing the vesicular and synaptic dopamine/norepinephrine ratio. We hypothesize that this physiologic effect could decrease the craving for nicotine or withdrawal symptoms.

The dopamine system is deeply involved in the nicotine dependence, withdrawal symptoms and response to treatment. The reinforcing effects of nicotine are mediated through its action on the cortico-mesolimbic dopamine neurons, enhancing the dopaminergic function (Johnson 2004). Nicotine dependent rats present a decrease in dopamine in the nucleus accumbens during nicotine withdrawal (Shoaib et al. 2004). Gilbert et al. (2004) reported in women who quit smoking a slowing of electroencephalographic frequency that was greater with stress, higher nicotine dependence, presence of DRD2 *Taq*I A1 allele and depressive traits. In addition, a placebo-controlled study showed that smokers who received Topiramate (a drug that antagonizes the ability of nicotine to increase dopamine activity) were more likely to become abstinent (Johnson 2004). All these results are coherent with our findings in which a genetic variation that increases dopamine availability (DBH-1021 T) seems to decrease cigarette consumption. These findings also support the hypothesis that the DRD2 *Taq*I A1 allele would increase smoking risk by decreasing the dopaminergic function.

A limitation of this study is the fact that we did not report the strict nicotine dependence diagnosis, but rather the information on daily use for at least one month. However, daily smoking is strongly related to nicotine dependence, since it usually starts when de-

pendence is already established (Mayhew et al. 2000; Wellman et al. 2004). Therefore, it is likely that most or all individuals referred here as persistent daily smokers are nicotine dependent. Population stratification is not likely to be a confounder in this study, because the samples were carefully limited to Brazilians of European descent. Moreover, the associations with smoking behavior were verified within the sample of blood donors, when all individuals were collected in the same institution and by the same interviewer.

This investigation reinforces the possible association between DRD2 and smoking risk and provides preliminary indication that the DBH gene may influence smoking behavior. The small effects observed stimulate further research on these candidate genes.

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