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PHARMACOGENETICS

CYP2B6 rs2279343 polymorphism is associated with smoking cessation success in bupropion therapy

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Abstract
Background Previous studies suggested that polymorphisms in the *CYP2B6* gene (which encodes an isoenzyme that metabolizes bupropion) and in the *ANKK1* gene (which is located in the *ANKK1*/*DRD2* gene cluster) might influence response to therapy. Thus, the aim of the present study was to evaluate whether the *CYP2B6* and *ANKK1* polymorphisms are associated with the response to smoking cessation therapies in patients from a smoking cessation assistance program.
Methods The cohort study enrolled 478 smokers who received behavioral counseling and drug therapy (bupropion, nicotine replacement therapy, and/or varenicline). Smoking cessation success was considered for patients who completed 6 months of continuous abstinence. Fagerström test for nicotine dependence (FTND) and Issa situational smoking scores were analyzed for nicotine dependence (ND). The *ANKK1* rs1800497, *CYP2B6*4* (rs2279343), *CYP2B6*5* (rs3211371), and *CYP2B6*9* (rs3745274) polymorphisms were genotyped by high resolution melting analysis or by restriction fragment length polymorphism.
Results Patients with *CYP2B6* rs2279343 wild-type AA genotype had higher success rate (48.0 %) compared with patients carrying AG or GG genotypes (*CYP2B6*4* variant) (35.5 %) on bupropion therapy. The AA genotype was associated with higher OR for success during bupropion therapy (OR = 1.92, 95 % CI = 1.08–3.42, $p = 0.03$) in a multivariate model. We did not observe significant differences in the FTND and Issa scores according to the studied polymorphisms.
Conclusion We showed that patients with *CYP2B6*4* (rs2279343) variant had lower success rate with bupropion. Likely, the *CYP2B6*4* variant, which leads to a rapid predicted metabolic phenotype for the isoenzyme, influences the pharmacological activity of bupropion. Our finding suggests that *CYP2B6*4* may be an important genetic marker for individualized bupropion pharmacotherapy.

Keywords Pharmacogenetics · *CYP2B6* gene · *ANKK1* gene · Bupropion

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Introduction

Tobacco is a leading cause of preventable morbidity and premature mortality worldwide, accounting for about six million deaths per year. If tobacco control policies are not strengthened, surveys show that tobacco induced mortality will reach 8.3 million in 2030, mostly affecting developing countries [1, 2]. Smoking is associated with the majority of cardiovascular diseases and cancer and with poor quality of life of smokers [2–4].

Studies report that treatments for smoking cessation using drugs are much more effective than those made without drugs

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[3–5]. Varenicline has been reported as an important drug in the pharmacotherapy of smoking cessation. The main targets are α4β2 subunits of the nicotinic acetylcholine receptors (nAChRs) not only promoting an antagonistic effect in the presence of nicotine but also acting as a partial agonist [6, 7]. Bupropion is the only antidepressant approved as a first-line drug for smoking cessation and its presumed mechanism of action involves modulation of dopaminergic and noradrenergic systems [8].

Twin and genome-wide association studies showed that genes have an important role in different smoking-related phenotypes [9–13]. Recent studies showed that the persistence of smoking and consequently the difficulty of smoking cessation have a great influence of genetic factors, with a heritability of approximately 50 % [14, 15]. Thus, it is clear that genetic information can lead us to a better understanding about effectiveness of anti-smoking therapies.

Pharmacogenetic studies identified associations of the *CYP2B6* and *ANKK1* polymorphisms with response to bupropion therapy [16–19]. Thus, we chose the main polymorphism in both genes. The first gene encodes the isoenzyme that metabolizes bupropion. The second, *ANKK1* (kinase domain and ankyrin repeat containing 1), encodes a protein involved in protein–protein interactions in the transduction pathways signal. It is located in the *ANKK1*/*DRD2* gene cluster on chromosome 11q23.2, and the *DRD2* gene encodes type 2 dopamine receptor [20–22].

In this context of personalized medicine, the main aim of the present study was to evaluate whether the *CYP2B6* and *ANKK1* polymorphisms are associated with response to smoking cessation therapies in patients from a smoking cessation assistance program.

Methods

Patient sample

This cohort study included 478 smoking patients from the PAF (Programa de Assistência ao Fumante/Smoker Assistance Program), Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo, Brazil, between January 2007 and September 2013. The study protocol was approved by the Institutional Ethics Committee (0022/11), and written informed consent was obtained from all participants prior to entering the study.

The study design was based on PAF, which consisted of an initial medical visit plus an average of four follow-up medical visits for 12 weeks. The follow-up was made by phone in patients who did not continue to come on scheduled medical visits. Clinical data and end-expiratory exhaled carbon monoxide (CO) were collected in all visits. Demographic, socioeconomic, and clinical data were acquired. Patients received behavioral counseling and drug treatment from physicians specialized in smoking cessation. Arbitrarily, bupropion plus NRT was prescribed for patients who smoked less than one cigarette pack per day, while varenicline was prescribed for patients who smoked one or more cigarette pack(s) per day or who failed in previous attempts with bupropion plus NRT. Our prescription to start co-administration of bupropion and varenicline was if the patient was unable to quit smoking after 2 or 3 weeks of starting varenicline use, or if the patient stopped smoking, but presented moderate or intense discomfort abstinence symptoms. Continuous abstinence (CA) was investigated after 6 months as of starting pharmacotherapy. In our analysis, we compared success group (patients who completed 6 months of CA confirmed by end-expiratory exhaled carbon monoxide) vs patients who did not achieved CA [23, 24].

We analyzed the Fagerström test for nicotine dependence (FTND) and Issa situational smoking score (Issa score). The FTND comprises six questions and classifies patients into five categories (ranging from 0 to 10 points): 1–2 points = very low dependence; 3–4 points = low dependence; 5 points = medium dependence; 6–7 points = high dependence; and 8–10 points = very high dependence. The FTND is used in many countries as a cheap, non-invasive, and easy way to assess ND [25]. The Issa score comprises four questions (ranging from 0 to 4 points) with one point for each affirmative response [23]. This score is based on the psychoactive effects of nicotine in the process of cognition, attention, concentration, mood, well-being, and pleasure [23].

Genotyping

Genomic DNA from subjects was extracted from peripheral blood following a standard salting-out procedure. Genotyping for the *ANKK1* rs1800497 (c.G2137A [*Taq* 1A]) was performed by polymerase chain reaction (PCR) followed by high resolution melting (HRM) analysis according to previous studies [26, 27]. Amplification of the fragment for the *ANKK1* rs1800497 was performed using the following primer sense and antisense: 5′- GGTGTGCAGCTCACTCCAT -3′ and 5′- ACAGCCATCCTCAAAGTGCT -3′ (71 base pairs). CYP2B6 (rs3745274, rs2279343, and rs3211371) polymorphisms were genotyped by PCR followed by restriction fragment length polymorphism previously described by Lang et al [28]. Supplementary Table 1 shows enzymes, reagents, and fragments for the polymorphisms. Six percent of the samples was randomly selected and reanalyzed as quality controls and gave identical results.

Statistical analysis

Continuous variables are presented as mean and standard deviation and categorical variables as frequencies. Chi-square

test was performed for the comparative analysis of categorical variables (general characteristics, smoking status rates, and categorized nicotine dependence scores) according to polymorphisms. The Student's *t* test was used for comparing general characteristics and FTND according to polymorphisms. Logistic regression univariate and multivariate models were performed to evaluate the odds ratio (OR) for success. Analysis for the *CYP2B6* (rs3745274, rs2279343, and rs321137) polymorphisms was performed using dominant models, i.e., *CYP2B6*4* rs2279343 (AA vs AG + GG), *CYP2B6*5* rs3211371 (CC vs CT + TT), and *CYP2B6*9* rs3745274 (GG vs GT + TT), as previously described [29]. For the *ANKK1* rs1800497, a dominant model (GG vs GA + AA) was adopted based on previous studies [17, 30]. Linear regression models for FTND score were conducted to evaluate the influence of polymorphisms in the presence of covariables. Linkage disequilibrium, Hardy–Weinberg equilibrium, and haplotype analysis were conducted with Haploview 4.0. statistical analyses were carried out using the SPSS software (v.16.0), with the level of significance set at $p \leq 0.05$.

Results

General characteristics and CYP2B6 and ANKK1 polymorphisms

Tables 1 and 2 show general and clinical characteristics according *CYP2B6*4* rs2279343 (AA vs AG + GG) polymorphism in the overall patient sample and in patients treated with bupropion, respectively.

The frequency of *CYP2B6* rs2279343 G, *CYP2B6* rs3745274 T, *CYP2B6* rs3211371 T, and *ANKK1* rs1800497 A alleles were 28.2, 29.6, 8.2, and 24.7 %, respectively. The genotypic distributions for the rs2279343, rs3745274, and rs1800497 were in accordance with Hardy–Weinberg equilibrium (HWE) ($X^2 = 0.42$; $p = 0.52$; $X^2 = 0.005$; $p = 0.94$; $X^2 = 0.15$; $p = 0.70$, respectively). The genotypic distribution for the rs3211371 polymorphism was not in HWE ($X^2 = 8.80$; $p = 0.003$).

Smoking cessation success according to CYP2B6 rs2279343

Table 3 shows the smoking cessation success rate of patients according to prescribed drugs and *CYP2B6* rs2279343 polymorphism. Patients with *CYP2B6* rs2279343 wild-type AA genotype had higher success rate (48.0 %) compared with patients carrying AG or GG genotypes (*CYP2B6*4* variant) (35.5 %) on bupropion therapy.

Table 4 shows a logistic regression analysis for smoking cessation success in the patient group treated with bupropion ($n = 237$). The AA genotype for *CYP2B6* rs2279343 polymorphism was associated with higher OR for success (OR = 1.92, 95 % CI = 1.08–3.42, $p = 0.03$) in a multivariate model for sex, age, race, FTND score, and co-administration of NRT. In the patient group treated with bupropion, some patients used

Table 1 Demographic and clinical characteristics of overall patients according to *CYP2B6* rs2279343 polymorphism

	AA ($n = 249$)	AG or GG ($n = 229$)	*p* value
Age (years)	55 ± 23	52 ± 15	0.11
Gender, female (%)	64.1	62.4	0.70
Self-declared race, White (%)	28.5	33.3	0.26
Scholarity, college (%)	31.7	36.7	0.57
Body mass index (kg/m^2)	27 ± 5	26 ± 5	0.11
FTND	6.8 ± 2.4	6.8 ± 2.6	0.83
FTND, ≥6 (%)	73.4	75.5	0.62
Issa score, ≥3 (%)	60.0	78.6	0.24
Hypertension (%)	41.4	41.5	0.98
Coronary artery disease (%)	15.3	17.0	0.60
Acute myocardial infarction (%)	18.9	17.5	0.69
Dyslipidemia (%)	38.2	40.6	0.58
Diabetes mellitus type 2 (%)	10.8	13.1	0.96
Depression (%)	19.7	21.0	0.73
Anxiety (%)	18.9	20.1	0.74
Obstructive pulmonary chronic disease (%)	15.7	14.8	0.80
Asthma (%)	2.8	1.3	0.25
Number of diagnosed diseases	2.4 ± 1.7	2.4 ± 1.7	0.99

FTND Fagerström test for nicotine dependence (range from 0 to 10 points) ($n = 478$), *Issa score* Issa situational smoking score (range from 0 to 4 points) ($n = 67$)

Table 2 Demographic and clinical characteristics of patients treated with bupropion according to *CYP2B6* rs2279343 polymorphism

	AA (n = 127)	AG or GG (n = 110)	p value
Age (years)	57 ± 24	53 ± 14	0.29
Gender, female (%)	69.3	67.3	0.74
Self-declared race, White (%)	43.7	44.2	0.93
Scholarity, (college)	24.6	21.6	0.76
Body mass index (kg/m^2)	27 ± 6	26 ± 5	0.06
FTND	6.5 ± 2.1	6.2 ± 2.6	0.38
FTND ≥6 (%)	69.2	66.3	0.65
Hypertension (%)	51.2	59.1	0.22
Coronary artery disease (%)	22.8	22.7	0.98
Acute myocardial infarction (%)	25.2	25.5	0.96
Dyslipidemia (%)	46.5	52.7	0.34
Diabetes mellitus type 2 (%)	11.0	12.7	0.86
Depression (%)	20.5	20.9	0.93
Anxiety (%)	23.6	30.9	0.21
Obstructive pulmonary chronic disease (%)	17.3	18.2	0.86
Asthma (%)	2.4	1.8	0.77
Number of diagnosed diseases	2.8 ± 1.7	3.0 ± 1.6	0.42

FTND Fagerström test for nicotine dependence (range from 0 to 10 points)

NRT (patch and/or gum, n = 192), and this variable was added as a covariate in the multivariate model.

Smoking cessation success according to CYP2B6*5, *6, *9, and ANKK1 rs1800497 polymorphisms

Smoking cessation success rate did not have significant differences among *CYP2B6*5* (rs3211371), **6* (rs2279343 + rs3745374), **9* (rs3745274), and *ANKK1* rs1800497 genotypes for all drug groups, even in a multivariate model.

For the group treated with bupropion, the *CYP2B6*5*, *CYP2B6*6*, and *CYP2B6*9* polymorphisms showed the following OR for success: 0.71 (95 % CI = 0.29–1.72, p = 0.44), 0.64 (95 % CI = 0.38–1.08, p = 0.11), and 0.62 (95 % CI = 0.35–1.09, p = 0.10), respectively. The AG or GG genotypes for *ANKK1* rs1800497 polymorphism showed OR for success of 0.82 (95 % CI = 0.46–1.48, p = 0.51) in a multivariate model.

Table 3 Smoking cessation success rate of patients according to prescribed drugs and *CYP2B6* rs2279343 polymorphism

Patient group	Success rate (%)		
	AA	AG or GG	p value
Overall (n = 478)	46.6	39.7	0.13
Varenicline (n = 164)	43.4	43.2	0.98
Varenicline plus bupropion (n = 77)	48.7	44.7	0.73
Bupropion (n = 237)	48.0	35.5	0.05

Linkage disequilibrium analysis shows that the studied *CYP2B6* polymorphisms are not in strong disequilibrium in our patient sample (Supplementary Figure 1). In a haplotype analysis, the GAC and GAT haplotypes for the *CYP2B6* were associated with smoking cessation success (p values: 0.04, 0.03, respectively).

FTND and Issa scores according to CYP2B6 and ANKK1 polymorphisms

We did not observe significant differences in the FTND and Issa scores according to rs2279343 polymorphism in the overall patient group (Table 1). In addition, studied polymorphisms were not associated with FTND score in multiple linear regression models (Supplementary Table 2).

Table 4 Logistic regression multivariate analysis for smoking cessation success in the patients submitted to bupropion therapy (n = 237)

Variables	OR	95 % CI	p value
AA genotype for the *CYP2B6* rs2279343	1.92	1.08–3.42	0.03
Gender (male)	1.81	0.96–3.40	0.07
Age	0.98	0.95–1.01	0.17
Self-declared race (White)	1.24	0.69–2.22	0.47
FTND score	0.97	0.86–1.09	0.59
Co-administration of gum and/or patch	1.04	0.51–2.15	0.91

FTND Fagerström test for nicotine dependence

Discussion

The main finding in the present study was the association of the *CYP2B6*4* with response to bupropion. Our hypothesis is that the pharmacological activity of bupropion could be altered by the functionality of the CYP2B6 isoenzyme with the *CYP2B6* rs2279343. This variant predicts a rapid metabolic phenotype for the isoenzyme which mediates almost exclusively the hydroxylation process of the drug [31, 32]. Thus, patients carrying *CYP2B6*4* AG or GG had lower success rate in the smoking cessation therapy.

The *CYP2B6* rs2279343 is a single-nucleotide polymorphism in the exon 5 resulting the change of the acid arginine for the lysine. Zanger et al. reported that this polymorphism leads to higher protein expression [33], and Kirchheiner et al. showed that individuals with the *CYP2B6*4* (AG or GG) had an increased bupropion clearance [34]. In this context, the hypothesis generated in this study is that patients with the AA genotype (wild type) for the rs2279343 have a predicted metabolic phenotype considered normal, maintaining an increased drug concentration in the plasma and a longer period of time in the organism, while patients with the AG or GG genotypes have a predicted metabolic phenotype considered rapid; consequently, the drug acts for a shorter time in the organism. Thus, carriers of AA genotype have higher success rate for anti-smoking therapy with bupropion. However, an interesting study indicated that hydroxybupropion, the main bupropion active metabolite, contributed to the pharmacologic effects of bupropion and that variability in response to bupropion treatment was related to variability in CYP2B6-mediated hydroxybupropion formation [35]. Thus, further studies are needed to confirm hypotheses which involve *CYP2B6* variants, metabolites, and pharmacological response.

No significant difference for the *CYP2B6*5*, **6*, **9*, and *ANKK1* rs1800497 polymorphisms was found with any studied phenotypes. In addition, no association of these polymorphisms with response to varenicline treatment was observed. Kirchheiner et al. and Burger et al. did not find associations of the *CYP2B6*5*, **6*, **9*, and *ANKK1* rs1800497 polymorphisms with the bupropion clearance compared with wild-type (*CYP2B6*1*). But, Lerman et al. showed that carriers of the **5* variant had less tobacco abstinence and bupropion reduced this effect in women, increasing the likelihood of smoking cessation [16]. For the **9* and **6* variants, some studies showed decreased enzymatic function [33, 36–40]. Regarding the *ANKK1* polymorphism, Lerman et al. and David et al. showed that smokers with GG genotype were associated with better response with bupropion [17, 30].

Regarding FTND score, Verde et al. did not find associations with **4* and **9* variants [9] and Bierut et al. and Singleton et al. did not find associations with *ANKK1* polymorphisms [41–43]. On the other hand, Riccardi et al. reported a higher frequency of patients with **6* variant in dependents of nicotine compared with non-dependents [44]. Erblich et al. showed that smokers carrying at least one *ANKK1* c.G2137A variant allele had higher craving to smoke compared with wild-type patients [45].

There are some limitations in this study. First, the sample size of patients treated with bupropion is relatively small. However, this study was effective to identify significant differences between genotypes, even in a multivariate analysis. Second, the range in the FTND score is small in this patient cohort because most of the patients were classified as having moderate to strong dependency. Third, a preliminary analysis of liver function of patients based on laboratory tests was not performed; however, patients were asked about the presence of liver diseases as an exclusion criterion.

In conclusion, we showed that patients with *CYP2B6*4* (rs2279343) variant had lower success rate with bupropion. Likely, the *CYP2B6*4* variant, which leads to a rapid predicted metabolic phenotype for the isoenzyme, influences the pharmacological activity of the bupropion. Our finding suggests that *CYP2B6*4* may be an important genetic marker for individualized pharmacotherapy of the bupropion.

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Conflict of interest The authors declare that they have no competing interests.

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