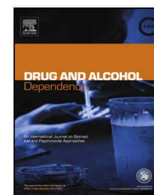
Drug and Alcohol Dependence 158 (2016) 139–146

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep



Full length article

Variation in *CYP2A6* and tobacco dependence throughout adolescence and in young adult smokers

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ARTICLE INFO

Article history:
Received 29 June 2015
Received in revised form 28 October 2015
Accepted 13 November 2015
Available online 21 November 2015

Keywords:
Nicotine
Addiction
Adolescent
Smoking
Genetics
CYP2A6
CYP2B6

ABSTRACT

Background: Smoking is influenced by genetic factors including variation in *CYP2A6* and *CYP2B6*, which encode nicotine-metabolizing enzymes. In early adolescence, *CYP2A6* slow nicotine metabolism was associated with higher dependence acquisition, but reduced cigarette consumption. Here we extend this work by examining associations of *CYP2A6* and *CYP2B6* with tobacco dependence acquisition in a larger sample of smokers followed throughout adolescence.
Methods: White participants from the Nicotine Dependence in Teens cohort that had ever inhaled ($n = 421$) were followed frequently from age 12–18 years. Cox's proportional hazards models compared the risk of ICD-10 tobacco dependence acquisition (score 3+) for *CYP2A6* and *CYP2B6* metabolism groups. Early smoking experiences, as well as amount smoked at end of follow-up, was also computed. At age 24 ($N = 162$), we assessed concordance between self-reported cigarette consumption and salivary cotinine.
Results: In those who initiated inhalation during follow-up, *CYP2A6* slow (vs. normal) metabolizers were at greater risk of dependence (hazards ratio (HR) = 2.3; 95% CI = 1.1, 4.8); *CYP2B6* slow (vs. normal) metabolizers had non-significantly greater risk (HR = 1.5; 95% CI = 0.8, 2.6). Variation in *CYP2A6* or *CYP2B6* was not significantly associated with early smoking symptoms or cigarette consumption at end of follow-up. At age 24, neither gene was significantly associated with dependence status. Self-reported consumption was associated with salivary cotinine, a biomarker of tobacco exposure, acquired at age 24 ($B = 0.37$; $P < 0.001$).
Conclusions: Our findings extend previous work indicating that slow nicotine metabolism mediated by *CYP2A6*, and perhaps *CYP2B6*, increases risk for tobacco dependence throughout adolescence.
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1. Introduction

Approximately 90% of smokers begin smoking in adolescence (O'Loughlin et al., 2014b; U.S. Department of Health and Human Services, 2012). A substantial proportion (~40–75%) of smoking behaviour is influenced by genetics (Broms et al., 2006; Vink et al., 2005). CYP2A6 inactivates nicotine, the principle psychoactive compound in cigarette smoke, to cotinine (Nakajima et al., 1996). Genetic variation in *CYP2A6* that reduces the rate of nicotine metabolism is associated with lower cigarette consumption (Malaiyandi et al., 2006; Wassenaar et al., 2011), dependence scores (Schnoll et al., 2014; Sofuoglu et al., 2012; Wassenaar et al., 2011), brain response to smoking cues (Tang et al., 2012), and greater cessation (Gu et al., 2000; Lerman et al., 2006; Schnoll et al., 2009), even in adolescence (Chenoweth et al., 2013). In adolescents, *CYP2A6* slow nicotine metabolism was also associated with an increased risk of tobacco dependence acquisition at young ages (from age 12 to 16 years; Al Koudsi et al., 2010; O'Loughlin et al., 2004), but slower escalation in nicotine dependence (Audrain-McGovern

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http://dx.doi.org/10.1016/j.drugalcdep.2015.11.017
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et al., 2007) and reduced cigarette consumption (O'Loughlin et al., 2004). In young adults, *CYP2A6* slow (vs. normal) metabolizers were less likely to be smokers (Schoedel et al., 2004). Together these findings suggest that while *CYP2A6* slow metabolism increases the risk of becoming a smoker in younger adolescence, slow metabolism also increases cessation, and reduces cigarette consumption in dependent smokers. However, it is not known whether *CYP2A6* slow metabolism increases smoking acquisition in later adolescence, a period during which a substantial amount of smoking uptake occurs (O'Loughlin et al., 2014b).

A small proportion (~10%) of nicotine's metabolism to cotinine occurs via a second enzyme, CYP2B6 (Al Koudsi and Tyndale, 2010). The *CYP2B6*6* allele, a prevalent haplotype (~25% frequency in Whites (Rotger et al., 2007)) is associated with lower CYP2B6 hepatic protein levels (Al Koudsi and Tyndale, 2010) and slower CYP2B6-mediated metabolism of bupropion and efavirenz (reviewed in (Thorn et al., 2010)). In adult smokers, *CYP2B6*6* was associated with lower abstinence rates in the placebo arm of a bupropion smoking cessation clinical trial; 15% of individuals with one or two copies of *CYP2B6*6* achieved abstinence, compared to 32% of *CYP2B6*1/*1* individuals (Lee et al., 2007a). In a separate study, the *CYP2B6*6* allele was more frequent in nicotine dependent individuals compared to those that were not dependent (32% vs. 22%, respectively; Riccardi et al., 2015). Whether *CYP2B6*6* also influences the risk for acquiring nicotine dependence in adolescence is not known.

Here we examined associations for *CYP2A6* and *CYP2B6* with tobacco dependence acquisition in a larger ($n > 400$) sample of adolescent smokers assessed four times each year across the entire adolescent period (age 12–18 years). We hypothesized that *CYP2A6* slow (vs. *CYP2A6* normal), and that *CYP2B6* slow (i.e., individuals with one or two copies of *CYP2B6*6*) (vs. *CYP2B6* normal) metabolizers would be at increased risk of acquiring dependence. We also hypothesized that a larger proportion of slow (vs. normal) metabolizers for each gene would report early smoking experiences, which are associated with the development of nicotine dependence (DiFranza et al., 2004). We also assessed cigarette consumption at the end of follow-up among dependent smokers, hypothesizing that *CYP2A6* slow (vs. *CYP2A6* normal) metabolizers would smoke fewer cigarettes; no association was expected between *CYP2B6* genotype groups. For both *CYP2A6* and *CYP2B6*, we further hypothesized that slow (vs. normal) metabolizers would be more likely to be dependent at end of follow-up. At age 24, we expected *CYP2A6* slow (vs. normal) metabolizers to be at lower risk of dependence, as *CYP2A6* slow metabolizers are less likely to be dependent smokers (vs. non-smokers) as adults (Schoedel et al., 2004). Finally, we hypothesized that *CYP2B6* slow (vs. normal) metabolizers would be more likely to be dependent at age 24, consistent with the higher frequency of *CYP2B6*6* in dependent (vs. non-dependent) adults (Riccardi et al., 2015).

Finally, an adjunct biochemical analysis to assess the validity of the self-reported cigarette consumption data was undertaken. We examined the construct-related validity of self-reported cigarette consumption against salivary cotinine, widely used as an objective biomarker of tobacco consumption (Connor Gorber et al., 2009), and also assessed its relationships with nicotine dependence and withdrawal scores.

2. Methods

2.1. Study population and data collection

As previously described (O'Loughlin et al., 2014a), 1294 adolescents from 10 secondary schools in Quebec were recruited in 1999 for the Nicotine Dependence in Teens (NDIT) cohort study (Montreal, Quebec, Canada). Self-report questionnaires were administered every three months during the 10-month school year over the five years of secondary school (grade 7–11), for a total of 20 survey cycles. Data from these 20 surveys for $n = 421$ ever smoking Whites were included in the current analyses of tobacco dependence acquisition and cigarette consumption. Previous analyses in this population included data only up to survey cycle 16 (age 15–16 years) for only 281 smokers (O'Loughlin et al., 2004). Two additional surveys (survey cycles 21 and 22) were administered three and six years, respectively, after high school graduation (O'Loughlin et al., 2014a). Data from survey 22, completed when participants were aged 24 years on average, were used, along with salivary cotinine, for additional analyses. Parents or guardians provided written informed consent and participants provided assent at baseline. Participants (who had attained legal age) provided informed consent during post-high school survey cycles. The study was approved by McGill University (Quebec, Canada), the Centre de recherche du Centre hospitalier de l'Université de Montréal (Quebec, Canada), and the University of Toronto research ethics board (Toronto, Canada).

2.2. Determination of CYP2A6 and CYP2B6 genotype

DNA was extracted from saliva or blood samples, and participants were genotyped for four *CYP2A6* alleles which occur at relatively high frequency (~1–8%) in Whites and have an established impact on reducing nicotine metabolism: *CYP2A6*2*, *CYP2A6*4*, *CYP2A6*9*, and *CYP2A6*12* (Benowitz et al., 2006; Chenoweth et al., 2013). Participants were grouped into *CYP2A6* normal, intermediate, or slow nicotine metabolism groups based on the predicted metabolic impact of each *CYP2A6* variant allele (Chenoweth et al., 2013). Participants were also genotyped for the *CYP2B6*6* allele, using a haplotyping method described previously (Lee et al., 2007a; Mwenifumbo et al., 2005); individuals with the *CYP2B6*1/*1* genotype were grouped as normal metabolizers, while those with one or two copies of the *CYP2B6*6* alleles were grouped as slow metabolizers. For genetic analyses, the sample was restricted to White ever-smokers in order to minimize possible effects of population stratification. *CYP2A6* genetic data were available for 421 White ever-smokers, while *CYP2B6* genetic data were available for 391 White ever-smokers.

2.3. Study variables

Data on early smoking experiences (symptoms of nausea and dizziness), tobacco/nicotine dependence (measured by the International Classification of Diseases (ICD)-10 and the modified Fagerstrom Tolerance Questionnaire (mFTQ) were collected, as were data on nicotine withdrawal, other nicotine dependence symptoms, and self-medication scores (Chenoweth et al., 2013). Briefly, nicotine withdrawal, other nicotine dependence symptoms, and self-medication scores were measured in six, 14, and five individual items, respectively, and assessed symptoms of withdrawal including irritability, restlessness, anxiety, craving frequency, and endorsement of statements that smoking improves energy level, affect, and stress (Chenoweth et al., 2013). Scores were pro-rated if there were fewer than half the items missing for an individual score. If half or more of the items were missing, the participant was assigned a missing value.

Three measures of cigarette consumption were used. The mean number of cigarettes smoked/month in the 3-month interval preceding each survey cycle was assessed by multiplying the average number of cigarettes smoked/day by the average number of days smoked/month in each of the three months and calculating the average monthly consumption (O'Loughlin et al., 2014c). The number of cigarettes smoked in the past week was assessed at survey

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