



Association of serotonergic pathway genes with smoking cessation in a Chinese rural male population

Qiang Wang^{a,b}, Suyun Li^{a,c}, Huijie Li^a, Chongqi Jia^{a,*}

^a Department of Epidemiology, Shandong University, Jinan, Shandong, PR China

^b Department of Epidemiology, Weifang Medical University, Weifang, Shandong, PR China

^c Department of Epidemiology and Health Statistics, School of Public Health, Qingdao University, Qingdao, Shandong, PR China



HIGHLIGHTS

- Rs1042173 of SLC6A4 was significantly related to smoking cessation among Chinese adult male smokers.
- Rs4570625 of TPH2 was significantly associated with smoking cessation among Chinese adult male smokers.
- There were significant interactions among SNPs of serotonergic pathway genes when these genes influenced smoking cessation.

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ABSTRACT

Introduction: Previous studies have found serotonergic pathway genes have inhibitory effects on dopamine system which may influence smoking addiction. This study examined the associations of serotonergic pathway genes (serotonergic receptor genes, solute carrier family 6 member4 and tryptophan hydroxylase gene) with smoking cessation.

Materials and methods: Male current and former smokers ($n = 819$) were recruited from 17 villages of three counties in Shandong province, China. DNA was extracted from the blood samples. Eleven single nucleotide polymorphisms (SNPs) in serotonergic pathway genes were genotyped. Multiple logistic regression was used to assess associations between SNPs and smoking cessation. Pearson's χ^2 test was performed to explore associations of haplotypes with smoking cessation. Multiple logistic regression was used to detect the interaction between SNPs on smoking cessation.

Results: In multiple logistic regression, rs1042173 of Solute carrier family 6 member 4 was significantly related to smoking cessation in additive and dominant model ($p = 0.03$ and 0.02 , respectively). Rs4570625 of tryptophan hydroxylase 2 was significantly associated with smoking cessation in dominant model ($p = 0.03$). Nine significant interactions were detected between SNPs in serotonergic pathway genes.

Conclusions: The present study reveals that serotonergic pathway genes were significantly related to smoking cessation. Future research should expand upon these findings to confirm them.

1. Introduction

Tobacco use is currently responsible for the deaths of about six million people across the world each year (WHO, 2015) and may cause 1 billion deaths this century (WHO, 2013). In China, the number of death resulting from smoking-related disease is up to 1 million every year and this number will be up to 3 million in 2050 (China, 2012). The prevalence of smoking among male adults was 56.1% and 49.2% in Chinese rural and urban areas, respectively (Yang, 2011). But the successful smoking cessation rates among male adults in Chinese rural and urban areas were just 7% and 8.7%, respectively (Hesketh, Lu, Jun, &

Mei, 2007). Thus, it is extremely important to develop effective tobacco control method in China, especially in rural areas.

Smoking addiction has a complex etiology generated by many factors including genetic and environmental factors (Sullivan & Kendler, 1999). Previous studies have revealed that about 56% variance of nicotine dependence is attributed to genetic influence (Li, Cheng, Ma, & Swan, 2003; Li et al., 2009). Then, another hypothesis needed to be validated is that whether smoking cessation is also influenced by genetic factors. The biological mechanism of smoking addiction is that nicotine increases the dopamine levels in the nucleus accumbens (Mansvelder & McGehee, 2002). Serotonergic (5-hydroxytryptamine, 5-

* Corresponding author at: Department of Epidemiology, Shandong University, Jinan 250012, Shandong, PR China.
E-mail address: jiachongqi@sdu.edu.cn (C. Jia).

HT) pathway genes have inhibitory effects on dopamine system and modulates dopaminergic neurotransmission based on previous researches (Kobayashi et al., 2011). Thus, serotonergic pathway genes may influence the functions of dopaminergic systems and the addiction of nicotine (Nielsen et al., 2008). Serotonergic pathway genes function through the cooperative effect of tryptophan hydroxylase (TPH) genes, serotonin reuptake transporters gene and serotonin autoreceptors genes (Best, Nijhout, & Reed, 2010). TPH genes are the rate-limiting enzyme in 5-HT synthesis and regulate the level of serotonin (Zhao, Huang, Li, Han, & Kan, 2015). Solute carrier family 6 member 4 (SLC6A4), serotonin reuptake transporters gene, affect 5-HT uptake function and concentration (Seneviratne, Huang, Ait-Daoud, Li, & Johnson, 2009). 5-hydroxytryptamine receptor2A (5-HT2A) gene modulates the nicotine's function of reinforcement and behavioral sensitization indirectly through dopamine system (do Prado-Lima et al., 2004). Therefore, the hypothesis is that these genes may be involved in the addiction of nicotine. It was reported that there were associations between serotonergic pathway genes and smoking (Li et al., 2015; Yang et al., 2013). However, the majority of previous researches paid attention to the relationships between serotonergic pathway genes and nicotine dependence rather than the relationships between serotonergic pathway genes and smoking cessation. Besides, previous studies were mostly carried out in European and/or African ancestry populations but few studies were available in Chinese population. Considered the different genetic effects on the etiology of smoking addiction among different ethnic populations, we aimed to examine the associations between serotonergic pathway genes and smoking cessation in a Chinese rural population.

2. Materials and methods

2.1. Definitions

According to the WHO guideline (World Health Organization, 1998), smokers are defined as those who have/had smoked 100 or more cigarettes (or the equivalent amount of tobacco) during their lifetime. Successful quitters refer to smokers who had not smoked at all for at least 2 years continuously at the time of the survey (Qian et al., 2010). Failed quit attempts refer to smokers who abstained for < 2 years continuously or relapsed after smoking cessation at the time of the survey.

2.2. Participants

This cross-sectional study was conducted among the persons residing in 17 villages of three counties (Ping Yin, Ju Nan, and Liang Shan) in Shandong province, China from April to May during 2013 when data was collected. Participants were male persons who was 18 years old or more and ever quit smoking spontaneously. Spontaneous quitting meant that smokers attempted to quit smoking without the help of medication and/or other treatment methods. All participants were face-to-face interviewed by the well-trained investigators and completed a questionnaire that was designed based on Global Adult Tobacco Survey (GATS) Core Questionnaire with Optional Questions (Global Adult Tobacco Survey Collaborative Group, 2008). Then, according to cessation situation based on questionnaires, participants are divided into three kinds: the first kind is smokers who had not smoked at all for at least 2 years continuously at the time of the survey, the second kind is smokers who have abstained for less than 2 years continuously at the time of the survey and the third kind is smokers who relapsed after smoking cessation at the time of the survey. On the basis of definition mentioned above, the first kind was successful smoking quitters; the second and third kinds were failed quit attempts. Blood samples were extracted from participants' vein. 819 blood samples were available and successfully genotyped (including 415 successful smoking quitters regarded as case group and 404 failed quit

attempts regarded as control group). The information about environmental and individual factors, e.g., education, age, race and other smoking-related information, was acquired by a questionnaire. This study was approved by the Ethics Review Committee of Shandong University and all participants provided informed consent.

2.3. Genotyping

Single nucleotide polymorphisms (SNPs) were selected on: (1) tagSNPs identified with Haploview software 4.2 based on the Chinese Han Beijing (CHB) population data of HapMap (HapMap Data Rel 27 PhaseII + III, Feb09, on NCBI B36 assembly, dbSNP b126) ($r^2 > 0.8$, Minor Allele Frequency > 0.05), (2) Functional relevance and importance (based on the CHB population data of the dbSNP database and 1000 Genomes (<http://browser.1000genomes.org/index.html>), and (3) SNPs related to smoking cessation in previous studies (Lerman et al., 2001; Polina, Contini, Hutz, & Bau, 2009; Reuter, Hennig et al., 2007; Sullivan, Jiang, Neale, Kendler, & Straub, 2001; White, Young, Morris, & Lawford, 2011; Yang et al., 2013; Yang & Li, 2014). Finally, eleven SNPs in serotonergic pathway genes were selected (Table 2).

DNA was extracted from the peripheral blood leukocytes using a kit from Tiangen Inc. (Beijing, China) (DP318). SNPs were genotyped by Bio Miao Biological Technology (Beijing) Co., Ltd. Primers and multiplex reactions were designed using AssayDesigner 3.1 and the RealSNP.com Website (<http://www.mysequenom.com>), respectively. MassArray (Sequenom, San Diego, CA, USA) was used for genotyping all markers using allele-specific matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry.

2.4. Statistical analysis

Pearson's χ^2 test was performed to compare the distribution of the categorical variables between case and control groups. If variance between case and control was equal, student *t*-test was used to examine the difference of means of continuous variables; otherwise, Wilcoxon rank sum test was used. Three genetic models, i.e., additive, dominant and recessive model (if T and G are the high-frequency and low-frequency allele of a SNP, respectively, additive, dominant and recessive model are TT vs GT vs GG, TT vs GT + GG and TT + GT vs GG, respectively) were employed. Multiple logistic regression was performed to explore the associations between SNPs and smoking cessation in three genetic models with age, number of years using cigarette products, occupation, education and reason for quitting as covariates. Haplotypes were defined by the SNPs in each gene with Haploview 4.2 software. The D' value of all blocks were 0.94 or more. The association of haplotype distributions with smoking cessation was assessed by Pearson's χ^2 test. Multiple logistic regression was used to detect interaction between SNPs on smoking cessation in three genetic models with age, number of years using cigarette products, occupation, education and reason for quitting as confounders. Statistical analyses were performed using Stata version 13.1. All reported probabilities (*P* value) were two sided. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic factors analysis

The demographic factors of participants were shown on Table 1. The case group showed significant higher age ($p < 0.01$) and fewer number of years using cigarette products ($p < 0.01$) compared with the control group. There was no difference between the case and control group in age of smoking onset and cigarettes per day. The distribution of occupation, education and reason for quitting between the case and control group was not significantly different.

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