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LETTER TO THE EDITOR

The Association Between Epoxide Hydrolase Genetic Variant and Effectiveness of Nicotine Replacement Therapy in a Han Chinese Population

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Dear Editor,

Nicotine is a psychoactive alkaloid that is thought to play a key role in addiction to commercial tobacco products [1] and cotinine is its primary metabolite [2]. Pharmacological treatment, such as nicotine replacement therapy (NRT), is a valid solution to this problem. Tobacco smoke contains many carcinogens such as nitrosamines [i.e., nicotine-derived nitrosamine ketone (NNK) and N-nitrosonornicotine (NNN)], and nicotine undergoes chemical conversion into NNK and NNN during the processes of curing and smoking [3]. Microsomal epoxide hydrolase (EPHX) is responsible for the metabolism of polycyclic aromatic hydrocarbons and the detoxification of pro-carcinogens in the process of smoking [4]. Therefore, in this study we aimed to investigate whether the genetic polymorphisms of EPHX, rs1051740 and rs2234922, are associated with the metabolic processing of cotinine in nicotine abstinence and craving.

Two hundred and eleven eligible participants took part in this study, and were randomly divided into active or placebo treatment groups in a double-blind manner (see Supplementary Materials). There were no significant demographic differences between the sublingual nicotine tablet and placebo groups except for age (Table S1). The distributions of the genotypes of the two loci did not significantly differ between the two groups. The genotypes of the participants deviated from Hardy–Weinberg equilibrium for both polymorphisms ($P < 0.01$ for rs1051740 and $P = 0.01$ for rs2234922).

One-way ANOVA was used between the genotypes with the 2 loci, and age was a covariate (rs1051740 $P < 0.05$ and rs2234922 $P > 0.05$) (Table S2). There was an interaction between age and genotype ($F = 3.90$, df $= 2$, $P = 0.02$) for rs1051740. The interaction of time, grouping (placebo/NRT), and genotype was significantly associated with the difference between the urinary cotinine concentration at the end of the 2nd month and baseline ($F = 5.20$, $P = 0.01$); the TT genotype was significantly associated with the interaction of time and grouping ($F = 14.12$, $P < 0.01$) for rs1051740. In rs1051740, the interaction of time, grouping, and genotype was significantly associated with the difference between the urinary cotinine concentration at the end of the 3rd month and baseline ($F = 4.33$, $P = 0.01$); and the TT genotype was significantly associated with the interaction of time and grouping ($F = 28.23$,

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$P < 0.001$). These results showed that the urinary cotinine concentration had decreased in the NRT group. For rs2234922, the interaction of time and grouping (placebo/nicotine) was significantly associated with the difference between the urinary cotinine concentration at the end of the 3rd month and baseline ($F = 4.13$, $P = 0.04$) (Table S3).

In the two-locus (rs1051740 × rs2234922) model using the generalized multifactor dimensionality reduction (GMDR) method, a significant difference in urinary cotinine concentration was found between baseline and the end of 2nd month in the active treatment group ($P = 0.01$), suggesting that the T allele of rs1051740 and the A allele of rs2234922 are potential factors that influence smoking abstinence.

The level of inhaled nicotine quickly rises in the blood and is rapidly distributed among all organs, crossing the blood-brain barrier and reaching the brain within 10 s [5]. Nicotine is only metabolized to a small extent in the lung and kidney. The major metabolites are cotinine (70%) and nicotine-*N*-oxide (4%). Cotinine is further metabolized, while ~17% is excreted unchanged in the urine. NRT is becoming more frequently used as an adjunct to smoking cessation. Assays of minor tobacco alkaloids, such as anabasine or anatabine, which are present in tobacco but not in pharmaceutical preparations of nicotine, may be of use in the future in determining the smoking status of NRT users.

A previous study has suggested that putative genotypes might influence EPHX1 activity, including the intermediate activity combination of rs1051740 × rs2234922 (CC × GG, TT × AA, and CT × AG) [6]. The TT genotype of rs1051740 was significantly associated with the interaction of time and grouping with cotinine levels between the end of the 2nd month and baseline, and the end of the 3rd month and baseline. The results suggested that urinary cotinine concentration had decreased at the end of the 2nd and 3rd months in the NRT group, which might be influenced by the allele T of rs1051740. However, the other genotypes, CC and CT, did not show an apparent effect of NRT. On the basis of the previous study, T is the high-activity *EPHX1* allele in rs1051740 [7], meaning that more nicotine might be converted to nitrosamines and less to cotinine, which could contribute to the decreased urinary cotinine concentration at the end of the 2nd and 3rd months. Using the GMDR method, the best high-risk SNP × SNP model identified was a two-locus genotype combination in this study. The genotype interaction between rs1051740 TT and rs2234922 AA showed that intermediate EPHX1 activity might be easy to modulate, in accordance with the previous study [6].

Several limitations need to be considered. First, the sample size was relatively small, resulting in the genotypes deviating from Hardy-Weinberg equilibrium at both loci. Second, individuals have different responses to NRT, some have a good response, while others may have no response [8]. Study of subgroups of smokers based on the genetic variation would provide further information. Third, the calculated interaction model is hard to explain. A previous study has reported that this might result from biological interactions between the variants or their products [9].

From the present study, we conclude that these two SNPs might play roles in the process of nicotine metabolism and abstinence, rs1051740 being more important; and *EPHX* SNPs (rs1051740 and rs2234922) are associated with the effectiveness of NRT. Clinical practice for NRT might be effective and precise for the specific genotypes carriers of *EPHX*.

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